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WO 02/053188 A1

(54) Title: COMPOSITIONS COMPRISING CYCLODEXTRINS AND NO-RELEASING DRUGS

(57) Abstract: The present invention relates to composition comprising cyclodextrins and a NO-releasing drug of formula, A-X-L-NO_n, wherein A is the radical deriving from a drug; X is a divalent radical connecting A with the NO-releasing group L-NO_n; L is selected from the group consisting of: O and S; n is 1 or 2.

Compositions comprising cyclodextrins and NO-releasing drugs

Field of the Invention

The present invention relates to compositions comprising a NO-releasing derivative of a pharmaceutically active compound.

Background of the Invention

In the last decade there has been a growing interest towards the preparation and the properties of compounds comprising a radical derived from a compound having pharmaceutical activity and a NO releasing group.

EP 670 82, EP 759 899 and EP 722 434 disclose nitric esters of non-steroidal antiinflammatory drugs (NSAIDs). These compounds present an improved activity and reduced side effects when compared to the drug without NO-releasing group.

WO 98/15568 discloses nitrate esters of corticoids. Also in this case a reduced toxicity is observed when the nitrate group is present.

Compounds comprising a radical derived from an antithrombotic drug and a NO-releasing group are described in WO 98/21193. The comparative data show that the introduction of the NO-releasing group causes an increase of activity of the drug.

WO 00/61537 discloses the preparation of drugs comprising a NO releasing group linked to, inter alia, anti-inflammatory, analgesic, bronchodilators, ACE-inhibitors, β -blockers, antineoplastic compounds. The use of a linking group presenting specific antioxidant properties allows the use of these drugs to patients affected by oxidative stress and/or endothelial dysfunction.

Thus, it is possible to say that the introduction of NO releasing groups has proven to be advantageous in many classes of drugs. However, the introduction of a NO releasing group often leads to a relevant drawback, i.e. a significant reduction in water solubility, that might lead to a slower adsorption rate of the drug in the human body. It is therefore desirable to find methods to improve the bioavailability of compounds comprising a radical derived from a compound having pharmaceutical activity and a NO-releasing group.

The use of cyclodextrin complexes in combination with NO releasing compounds is known from WO 95/29172. In that case, however, there was no radical derived from a compound having pharmaceutical activity in the molecule complexed with Cyclodextrin and, furthermore, the problem was to render the molecule stable to degradation. Thus, both the

type of compound and the technical problem solved by the patent application are quite different from the present case.

Summary of the invention

The present invention relates to compositions for pharmaceutical use comprising a cyclodextrin and a compound comprising a radical derived from a compound having pharmaceutical activity and a NO releasing group.

Detailed description of the invention

The invention relates to compositions comprising cyclodextrins and a NO-releasing drug of formula



wherein A is the radical deriving from a drug;

X is a divalent radical connecting A with the NO-releasing group;

L is selected from the group consisting of: O and S; preferably it is O;

n is 1 or 2, preferably it is 2.

15 The syntheses of these compounds is described in the following patents, which are herewith incorporated by reference: US 5,861,426, WO 98/15568, US 5,621,000, WO 00/61537, WO 00/61541, WO 00/61604, US 5,703,073, US 6,043,233, US 6,057,347.

Cyclodextrins are cyclic oligosaccharides constituted by the union of from 6 to 12 glucose units through $\alpha(1,4)$ bonds. The word CD, used to indicate them, is usually preceded by a Greek letter that indicates the amount of glucose units (α corresponds to 6, β corresponds to 7, and so on).

A characteristic parameter of CDs is the diameter of the cavity wherein the compound is complexed.

For many purposes α -CD have a too small cavity (5 Å) to complex molecules of a medium size. This is why for many applications β -CD is preferred (diameter: 6 Å). The drawback of β -CD is its low solubility in water (18.5 g/l). To overcome the problem, probably caused by inter- and intramolecular hydrogen bonds between the hydroxyl groups, β CD derivatives have been prepared which present a considerably higher water solubility. In fact, it is known that the hydroxyl groups in the glucose units of CDs can be selectively reacted to prepare ethers, esters, ionic ethers (see for example the review "Physicochemical Characteristics and Pharmaceutical uses of Cyclodextrin Derivatives" D. Duchene et al., Pharmaceutical Technology International, June 1990).

The cyclodextrins to be used in combination with the compounds of formula A-X-L-NO_n are not particularly limited. Preferred examples of cyclodextrins useful in the present invention are: α-CD, dimethyl α-CD, trimethyl α-CD, β-CD, dimethyl β-CD, trimethyl β-CD, 2-hydroxypropyl β-CD, 3-hydroxypropyl β-CD, 2,3-dihydroxypropyl β-CD, γ-CD, dimethyl γ-CD, trimethyl γ-CD and polymeric CD.

In each particular case, it is possible to determine, with a few trials, which one is the most suitable cyclodextrin to be used in combination with a specific drug.

The molar ratio between the drug and the cyclodextrin can vary in a broad range. Preferably it is comprised between 1:10 and 10:1, more preferably between 3:1 and 1:3.

The composition according to the invention can be prepared in different ways. For example, it is possible to mix together the cyclodextrin and the NO-releasing drug in water. Due to the low solubility of most drugs, the drug is partly or fully dissolved when complexed with the CD. The solution is then dried and the solid recovered. It is also possible to use a cosolvent (e.g. ethanol) which is miscible with water and that solubilizes the drug. In another embodiment it is also possible to isolate the pure complex by using a two phase system: a lipophilic solvent wherein the drug is soluble, and water. The CD dissolves in the water phase, the drug in the lipophilic phase. The complex CD-drug is formed at the interphase. If it is soluble in water, it is recovered from the water phase.

Finally, it is also possible to simply mix the drug and the CD in the solid state by using mixing and/or milling means well known in the art.

In a preferred embodiment, the drug used in the compositions according to the present invention, is selected from the following classes of compounds:

non steroidal antiinflammatory and analgesic drugs, antibacterial (antibiotics), antiviral, steroids, antineoplastic, β-adrenergics (agonists and blockers), antihyperlipoproteinemic, bone resorption inhibitors.

Non limiting examples of non-steroidal anti-inflammatory and analgesic drugs are:

Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, Paracetamol, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Ketorolac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen, Bermoprofen, CS-670, Zaltoprofen, Tenoxicam, Piroxicam, Meloxicam, Tenidap, Aceclofenac, Acemetacin, 5-amino-acetylsalicylic acid, Alclofenac, Alminoprofen, Amfenac, Bendazac, α-bisabolol,

- Bromosaligenin, Bucloxic acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Diflunisal, Ditazol, Enfenamic acid, Etofenamate, Felbinac, Fenclozic acid, Fendosal, Fentiazac, Fepradinol, Flufenamic acid, Flunixin, Flunoxaprofen, Flurbiprofen, Glucametacin, Glycol salicilate, Ibuproxam, Isofezolac, Isoxepac, Isoxicam, Lornoxicam, Meclofenamic acid, 5 Mefenamic acid, Metiazinic acid, Niflunic acid, Oxaceprol, Oxaprozin, Oxyphenbutazone, Parsalmide, Perisoxal, Olsalazine, Pirprofen, Protizinic acid, Salacetamide, Salicilamide O-acetic acid, Salsalate, Suxibuzone, Tiaramide, Tinoridine, Tolfenamic acid, Tropesin, Xenbucin, Ximoprofen, Zomepirac, Tomoxiprol.
- 10 Non limiting examples of antibacterials (antibiotics) are:
- Metronidazolo, Ethambutol, Cycloserina, Cloxyquin, Negamycin, Nitroxoline, Mupirocin, Myxin, Novobiocin, Spectinomycin, Sulbactam, Tigemonam, Tubercidin, Nifurpirinol, Nifurprazine, Glyconiazide, Isoniazide, Opiniazide, Clofazamine, Meclocycline, Minocycline, Sancicline, Tetraciline, Oxytetracycline, Chlortetracycline, Demeclocycline, Methacycline, 15 Doxycycline, Clomocycline, Cinoxacin, Rolitetracycline, Pipaciclyne, Guamecycline, Lymecyclinem, Apiciclyne, Nalidixic acid, Cyprofloxacin, Enoxacin, Floroxacin, Pipemidic acid, Difloxacin, Perfloxacin, Enrofloxacin Nadifloxacin, Grepafloxacin, Lomefloxacin, Sparfloxacin, Clinafloxacin, Tosufloxacin, Trovafloxacin, Ofloxacin, Flumequine, Pazufloxacin, Rufloxacin, Norfloxacin, Cefroxadine, Cephradine, Cefaclor, Cefadroxil, 20 Cefprozil Cefatrizine, Cefpiramide, Cephalexin, Cephaloglycin, Loracarbef, Pivcephalexin, Cephamandole, Moxalactam, Cefclidin, Cefepime, Cefuzopran, Ceftibuten, Cefpodoxime Proxetil, Cefotaxime, Cefcapene Pivoxil, Cefodizime, Ceftiofur, Ceftriaxone, Cefditoren, Cefmenoxime, Cefteram, Cefuzonam, Cefdinir, Cefetamet, Cefixime, Cefpirome, Ceftazidine, Cefminox, Cephalosporin, Cefotiam, Ceforanide, Cefazolin, Ceftizoxime, Cefazedone, 25 Cefonicid, Ceftezole, Cephacetrile, Cephapirin, Fenbenicillin, Hetacillin, Quinacillin, Pivampicillin, Aspoxicillin, Mezlocillin, Amoxicillin, Ampicillin, Epicillin, Phenethamate Cyclacillin, Amdinocillin, Penicillin N, Apalcillin, Bacampicillin, Sultamicillin, Talampicillin, Lenampicillin, Benzyl penicillic acid, Carbenecillin, Carindacillin, Clometocillin, Cloxacillin, Dicloxacillin, Floxacillin, Metampicillin, Methicillin, Oxacillin, 30 Penicillin O, Penicillin V, Pheneticillin, Piperacillin, Propicillin, Sulbenicillin, Ticarcillin, Meropenem, Panipenem, Imipenem, Aztreonam, Carumonon, Sulfabenzamide, Sulfacetamide, Sulfachloropyridazine, Sulfacytine, Sulfadiazine, 4'-(Methylsulfamoyl)sulfanilamide, Sulfadicramide, Sulfadoxine, Sulfamethoxine,

- Sulfaethidolo, Sulfaguanole, Sulfalene, Sulfamerazine, Sulfameter, Sulfamethazine, Sulfamethizolo, Sulfamethonide, Sulfamethoxazole, Sulfamethoxypyridazine, Sulfamethylthiazole, Sulfametrole, Sulfamoxolo, Sulfanilamide, N⁴-Sulfanilylsulfanilamide, Sulfanilyurea, N-Sulfanil-3,4-xylamide, Sulfaperine, Sulfaphenazole, Sulfaproxyline,
- 5 Sulfapyrazine, Sulfapyridine, 4-Sulfanilamido salicylic acid, Sulfasomizole, Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfisomidine, Sulfisoxazole, Acetyl sulfamethoxypyrazine, Sulfaguanidine, Mafenide, Succisulfone, p-Sulfanylbenzylamine, Dapsone, Acediasulfone, Thiazolsulfone, 2-p-Sulfanilylanilino-ethanol, Benzylsulfamide, p-Aminosalicylic acid, p-Aminosalicylic acid hydrazide, Phenyl aminosalicylate, 4-4'-sulfinyldianiline, Clindamycin,
- 10 Lincomycin, Josamycin, Midecamycins, Rokitamycin, Spiramycins, Mikamycin B, Rosaramycin, Azithromycin, Clarithromycin, Erytromycin, Dirithromycin, Amikacin, Arbekacin, Dibekacin, Tobramycin, Dihydrostreptomycin, Streptomycin, Deoxydihydrostreptomycin, Trospectomycin, Spectinomycin, Micronomicin, Netilmicin, Apramycin, Sisomicin, Neomycin, Paromomycin, Ribostamycin, Rifampin, Rifapentine.
- 15 Sulfachrysoidine, Sulfamidochrysoidine, Salazosulfadimidine.

Non limiting examples of antiviral drugs are:

- Acyclovir, Amantadine, Cidofovir, Cytarabine, Didanosine, Dideoxyadenosine, Edoxuridine, Famciclovir, Floxuridine, Ganciclovir, Idoxuridine, Indanavir, Lamivudine, Kethoxal,
- 20 MADU, Penciclovir, Ribavirin, Sorivudine, Stavudine, Trifluridine, Valacyclovir, Vidarabine, Xenazoic acid, Zalcitabine, Zidovudine.

Non limiting examples of steroids are:

- Budesonide, Hydrocortisone, Aclomethasone, Algestone, Beclomethasone, Betamethasone,
- 25 Chlorprednisone, Clobetasol, Clobetasone, Clcortolone, Cloprednol, Cortisone, Corticosterone, Deflazacort, Desonide, Desoximethasone, Dexamethasone, Diflorasone, Difluocortolone, Difluprednate, Fluazacort, Flucoronide, Flumethasone, Flunisolide, Fluocinolone acetonide, Flucinonide, Fluocortin butyl, Fluocortolone, Fluorometholone, Fluperolone acetate, Fluprednilene acetate, Fluprednisolone, Flurandrenolide, Formocortal,
- 30 Halcinonide, Halobetasol propionate, Halomatasone, Halopredone acetate, Hydrocortamate, Loteprednol etabonate, Medrysone, Meprednisone, Methylprednisolone, Mometasone furoate, Paramethasone, Prednicarbate, Prednisone, Prednisolone 21-diethylaminoacetate, Prednisolone sodium phosphate, Prednival, Prednylidene, Rimexolone, Triamcinolone,

Triamcinolone acetonide, 21-Acetoxypregnenolone, Cortivazol, Amcinonide, Fluticasone propionate, MaziPredone, Tixocortol, Triamcinolone hexacetonide, Ursodeoxycholic acid, Chenodeoxycholic, Mytatrienediol, Ethynil Estradiol, Estradiol, Mestranol.

5 Non limiting examples of antitumoral drugs are:

Antacitabine, Anthramycin, Azacitidine, 6-Azaauridine, Carubicin, Chlorambucil, Chlorozotocin, Cytarabine, Daunomicin, Defosfamide, Denopterin, Doxifluridine, Doxorubicin, Droloxifene, Edatrexate, Eflornithine, Enocitabine, Epirubicin, Epitiostanol, Etanidazole, Etoposide, Fenretinide, Fludarabine, Fluorouracil, 10 Gemcitabine, Hexestrol, Idarubicin, Lonidamine, Melphalan, 6-mercaptopurine, Methotrexate, Mitoxantrone, Mycophenolic acid, Pentostatin, Pirarubicin, Piritexim, Podophyllic acid, Puromycin, Retinoic acid, Roquinimex, Streptonigrin, Teniposide, Tenuazonic acid, Thiamiprine, Thioguanine, Tomudex, Topotecan, Trimetrexate, Tubercidin, Ubenimex, Zorubicin.

15

Non limiting examples of β -adrenergic compounds are:

Albuterol, Bambuterol, Bitoterol, Carbuterol, Clenbuterol, Chlorprenalina, Dioxethedrine, Ephedrine, Epinephrine, Etafredine, Ethylnorepinephrine, Fenoterol, Isoetharine, Isoprotenerol, Mabuterol, Metaproterenol, Pirbuterol, Salmeterol, Soterenol, Terbutalina, 20 Tuloterol, Procaterol, Bufetalol, Acebutolol, Alprenolol, Arotinolol, Atenolol, Betaxolol, Bevantolo, Bucumolol, bufuralol, Bunitrolol, Bupranolol, Carazolol, Carteolol, Celiprolol, Epanolol, Indenolol, Mepindolol, Metoprolol, Nadolol, Nifenalol, Penbutolol, Pindolol, Pronethalol, Propanolol, Sotalol, Timolol, Toliprolol, Butofilol, Cervedilol, Cetamolol, Dilevalol, Esmolol, Labetalol, Metipranolol, Moprolol, Nebivolol, Oxprenolol, Practolol, 25 Sulfinalol, Tertatolol, Tilisolol, Xibenolol, Eprozinol, Etophylline, Exoprenaline, Propoxyphilline, Reproterol, Rimiterol, 1-Teobrominacetic acid, Tetroquinol, Nadoxolol.

Non limiting examples of antihyperlipoproteinemic compounds are:

Atovarstatin, Cilastatin, Dermostatin A, Dermostatin B, Fluvastatin, Lovastatin, Mevastatin, 30 Nystatin A₁, Pentostatin, Pepstatin, Sinvastatin

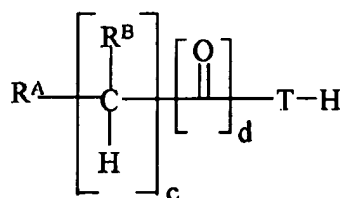
Non limiting examples of bone resorption inhibitors are:

Alendronic acid, Butedronic acid, Etidronic acid, Oxidronic acid, Pamidronic acid, Risedronic acid.

The chemical formula of the above listed compounds is reported on the Merck Index, Twelfth Edition.

5 Preferred drugs useful in the present invention are selected from the following formulas:

i)

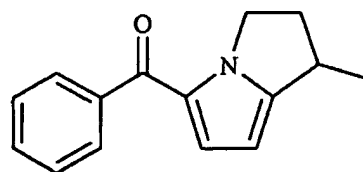
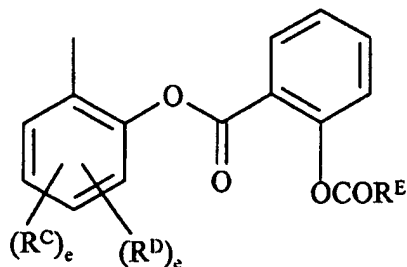
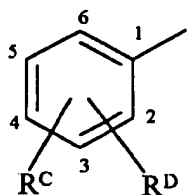


where **c** and **d** are independently 0 or 1;

10 **T** is selected from the group consisting of: O, NH and S;

R^B is selected from the group consisting of H, a linear or branched C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl; preferably **R^B** is H, an alkyl having from 1 to 4 carbon atoms, most preferably **R^B** is CH₃

When **c** is equal to 0, **d** is 1, **R^A** is selected from the group consisting of:



15

wherein:

R^C is selected from the group consisting of amino, R^ECONH-, OCOR^E group, and the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or
20 totally hydrogenated, containing one or more heteroatoms independently selected from the group consisting of O, N, and S;

R^E is selected from the group consisting of methyl, ethyl and a linear or branched C₃-C₅ alkyl;

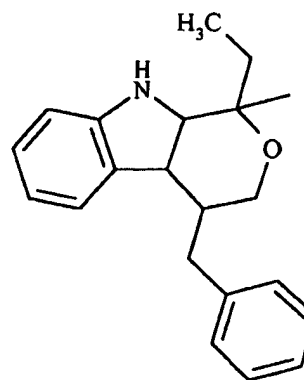
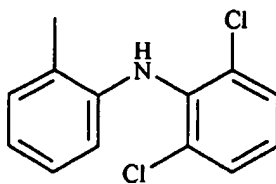
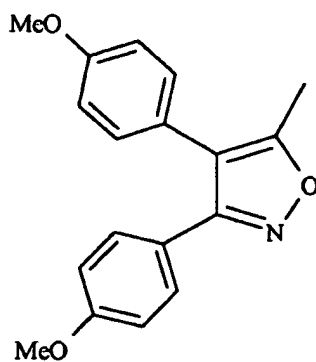
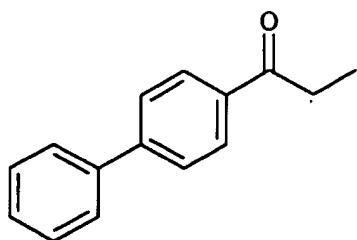
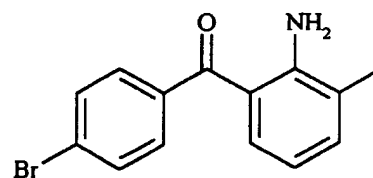
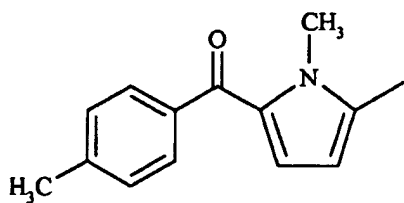
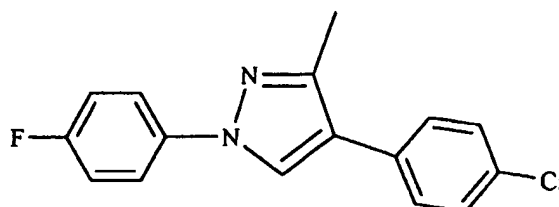
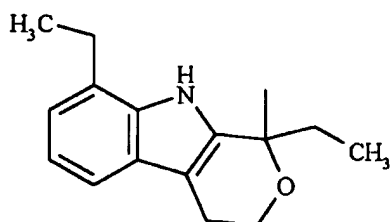
R^D is H, OH, halogen, a linear or when permissible branched alkyl having 1 to 4 atoms, a linear or when permissible branched alkoxy having 1 to 4 atoms, a linear or when permissible

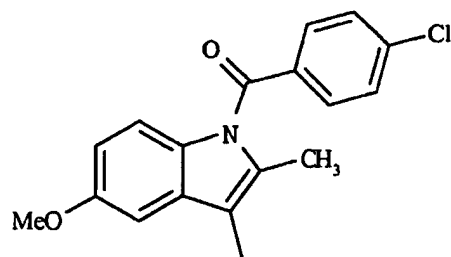
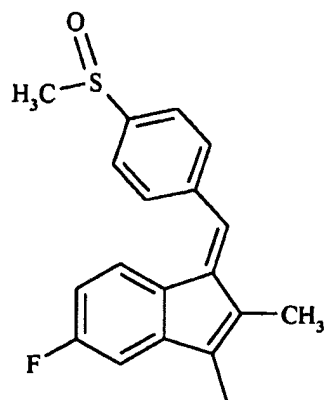
branched perfluoroalkyl having 1 to 4 carbon atoms, for example trifluoromethyl, amino, mono- or di-(C₁-C₄) alkylamino;

e is 0 or 1;

when c is equal to 1, d is equal to 1, R^b is hydrogen, R^a is selected from the group consisting

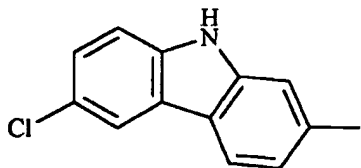
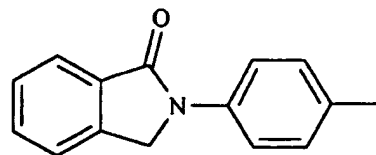
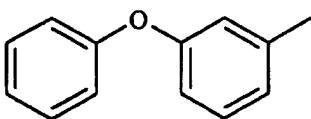
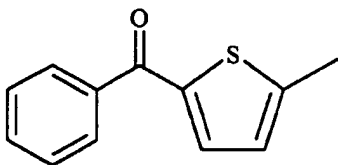
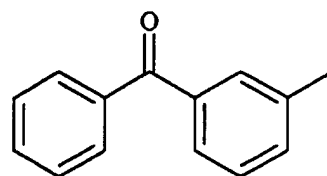
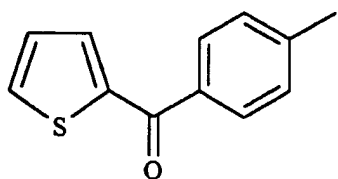
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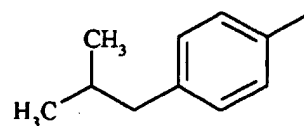
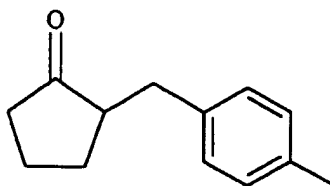
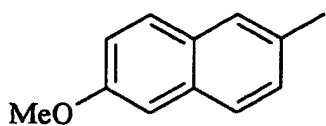


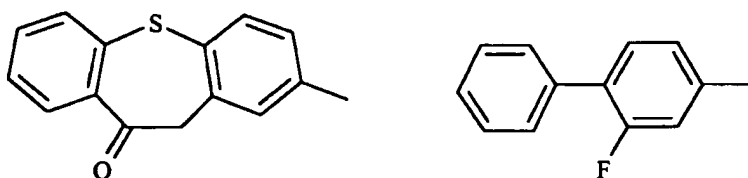
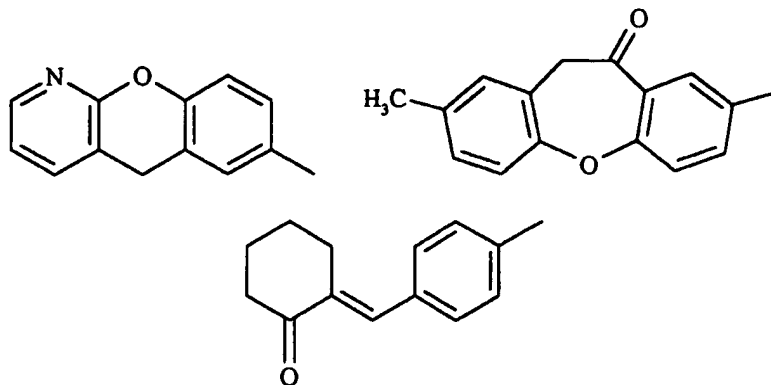
when c is equal to 1, d is equal to 1 and R^B is CH_3 , R^A is selected from the group consisting of:

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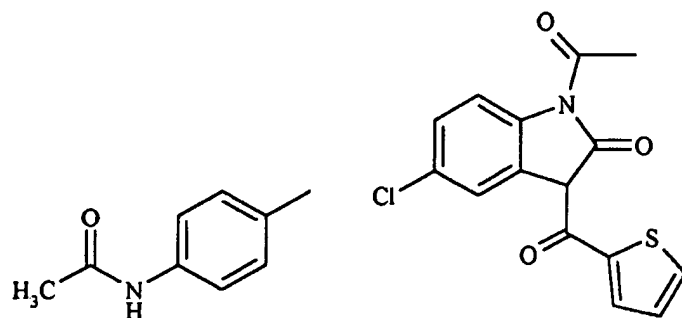
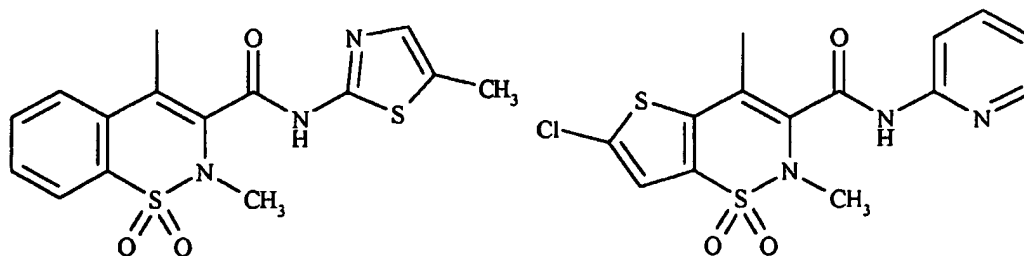
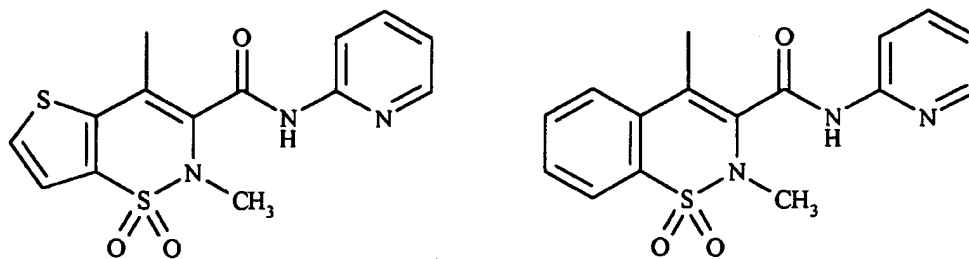
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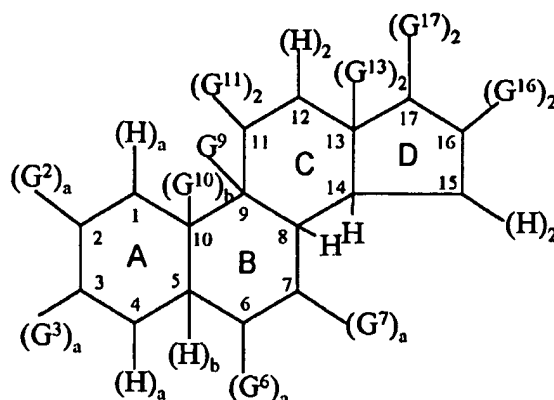
5

when **c** is equal to 0, **d** is equal to 0, **R^A** is selected from the group consisting of:



10

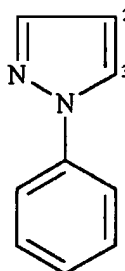
ii)



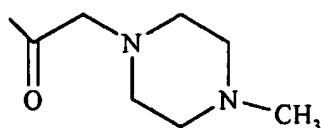
wherein:

at the position 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 5-10 there may be a double bond; the ring A is

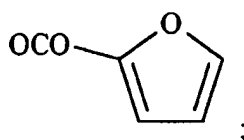
5 optionally an aromatic ring;

a is equal to 1 or 2, **b** is equal to 0 or 1;each G^2 is independently selected from the group consisting of H, Cl, Br;each G^3 is independently selected from the group consisting of H, O-CH₃, O-CH₂-CH₂-Cl, OH; two G^3 can form a carbonyl group with the C³ atom;10 one G^2 and one G^3 can unite to form a ring of formulawherein C²=C³ are part of the steroid structure;each G^6 is independently selected from the group consisting of H, Cl, F, CH₃, -CHO;each G^7 is independently selected from the group consisting of H, Cl, OH;15 each G^9 is independently selected from the group consisting of H, Cl, F; G^{10} is selected from the group consisting of H, Cl, F, CH₃, -CHO;each G^{11} is independently selected from the group consisting of H, OH, , Cl; two G^{11} can form a carbonyl group with the C¹¹ atom;each G^{13} is independently selected from the group consisting of H, CH₃;20 each G^{16} is independently selected from the group consisting of H, CH₃, OH; two G^{16} can form a vinyl group with the C¹⁶ atom;

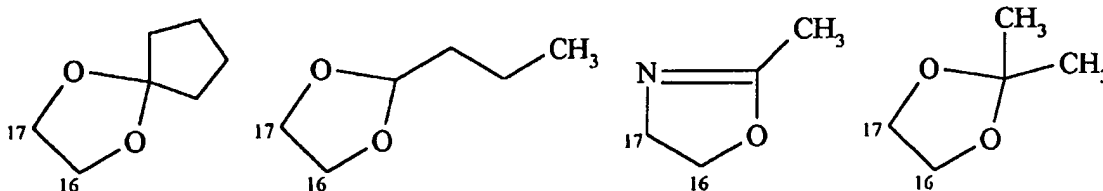
- each G^{17} is independently selected from the group consisting of H, OH and a monovalent radical comprising from 1 to 20 carbon atoms and from 0 to 5 oxygen, sulfur, nitrogen, halogen atoms; preferably it is H, OH, CH_3 , $C\equiv CH$, $CO-R-OH$, $CO-RH$, $CO-R-Cl$, $OCO-RH$, $CO-COO-RH$, $R-COOH$, $CH(OH)R-OH$, $COO-R-Cl$, $OC(O)O-RH$, $CO-R-SH$, $CO-R-O-CO-R-N(CH_2CH_3)_2$, $CO-SCH_2F$, $CO-R-OCORH$,



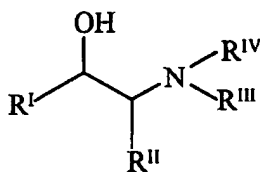
wherein R is a C_1 - C_{20} linear or branched alkylene radical, and



- two G^{17} can form a carbonyl group with the C^{17} atom;
 10 one G^{16} can unite with a G^{17} group to form, together with C^{16} and C^{17} the following groups:



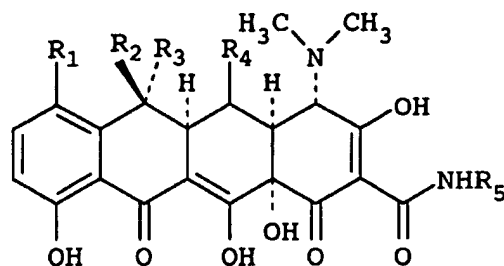
iii)



- 15 R^I is monovalent radical comprising from 6 to 20 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, chlorine, bromine, fluorine; examples of functional groups which are present in the radical R^I are the following: phenoxy, phenyl, thiazolyl, quinol-5-on-yl, pyridyl, tiofuranyl, tetrahydrofuranyl;
 R^{II} is selected from the group consisting of hydrogen and linear or branched alkyl having
 20 from 1 to 4 carbon atoms, preferably R^{II} is selected from the group consisting of H, CH_3 and CH_3CH_2
 R^{III} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms, preferably R^{III} is selected from the group consisting of H and CH_3 ;

R^{IV} is selected from the group consisting of hydrogen, a linear or branched alkyl having from 1 to 4 carbon atoms and a substituted aryl; preferably R^{IV} is selected from the group consisting of tert-butyl and isopropyl;

5 iv)



wherein:

R_1 is selected from the group consisting of H, Cl and dimethylamino,

10 R_2 is selected from the group consisting of H, OH,

R_3 is selected from the group consisting of H, CH_3 ,

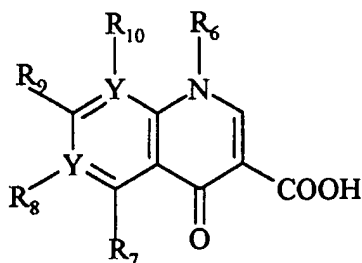
R_2 and R_3 together can be a methylene group ($CH_2=$),

R_4 is selected from the group consisting of H, OH,

R_5 is selected from the group consisting of H, CH_2OH and a monovalent radical containing

15 from 5 to 20 carbon atoms and from 1 to 8 nitrogen atoms; the radical can further comprise other functional groups such as carboxyl and hydroxyl.

v)



20

wherein

each Y is independently selected from the group consisting of C and N,

R_6 is selected from the group consisting of cyclopropyl, phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-fluoroethyl and ethyl;

R_7 is selected from the group consisting of H, amino, methyl,

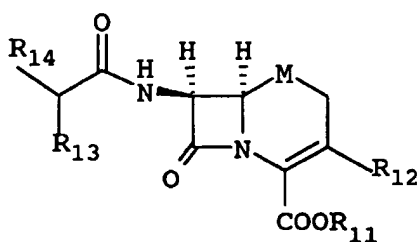
R_8 is selected from the group consisting of H and F;

R_9 is selected from the group consisting of H, methyl and a monovalent radical containing from 1 to 20 carbon atoms and from 1 to 4 nitrogen atoms;

5 R_{10} is selected from the group consisting of H, Cl and F;

R_6 e R_{10} can unite to form an optionally substituted six membered ring optionally containing up to two heteroatoms selected from the group consisting of oxygen and sulfur:

vi):



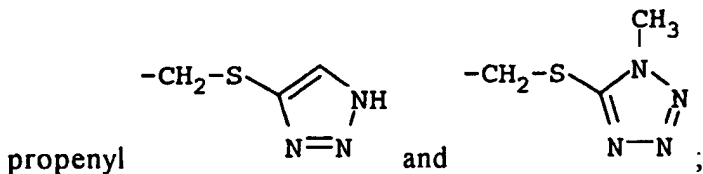
10

wherein

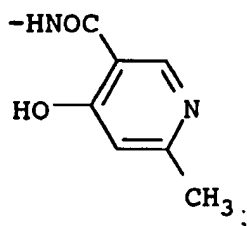
M is selected from the group consisting of sulfur, carbon or oxygen;

R_{11} is selected from the group consisting of H, pivaloyloxymethyl,

15 R_{12} is selected from the group consisting of chlorine and a monovalent radical containing from 1 to 5 carbon atoms, from 0 to 5 nitrogen atoms and from 0 to 1 sulfur atoms; preferably it is selected from chlorine, methyl, acetyloxymethyl, 2-



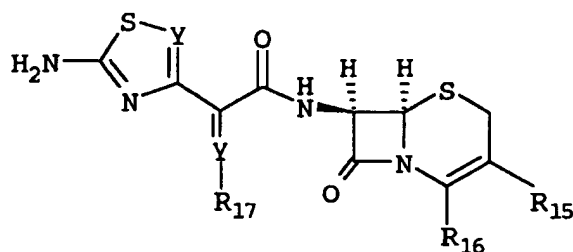
20 R_{13} is selected from the group consisting of amino, hydroxyl and monovalent radical containing from 1 to 10 carbon atoms, from 0 to 5 oxygen atoms and from 0 to 5 nitrogen atoms; preferably it is selected from the group consisting of amino, hydroxyl, carboxyl and



R₁₄ is an unsaturated C₆ ring, optionally substituted; preferably it is selected from the group consisting of phenyl, 1,4-cyclohexadienyl and 4-hydroxyphenyl.

5

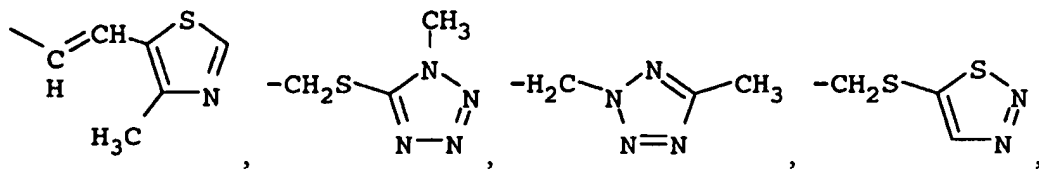
vii)

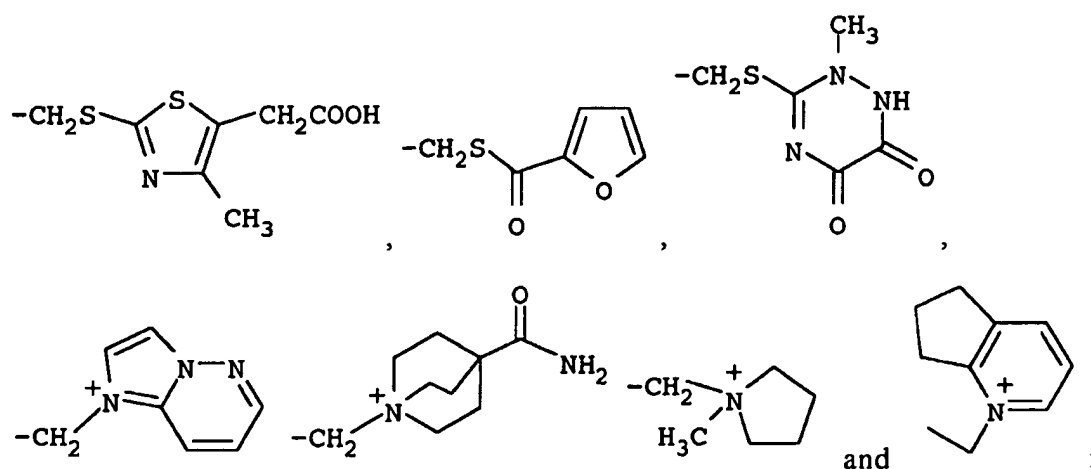


wherein:

10 each Y is independently selected from the group consisting of carbon and nitrogen

R₁₅ is selected from the group consisting of hydrogen and a monovalent radical containing from 1 to 12 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of H, methyl, ethyl, ethenyl, NH₂COOCH₂-, CH₃COOCH₂-,
 15 pyridilmethylene and

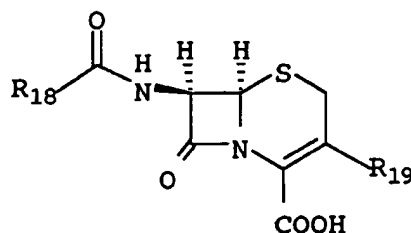




R_{16} is a monovalent radical containing from 1 to 10 carbon atoms and from 2 to 8 oxygen atoms; preferably it is selected from the group consisting of carboxyl, (CH₃)₃CCOOCH₂OCO- and (CH₃)₂CHOCOOCH(CH₃)OCO-; when R_{15} is a quaternary ammonium cation, R_{16} is optionally a -COO⁻;

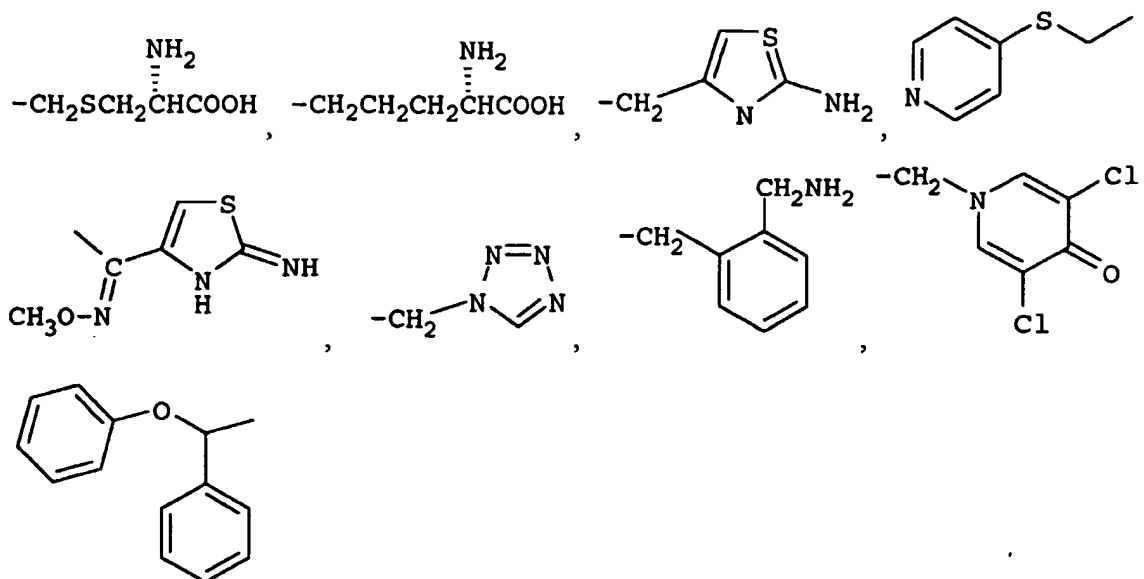
R_{17} is selected from the group consisting of -OH and a monovalent radical containing from 1 to 12 carbon atoms and from 0 to 4 oxygen atoms, preferably it is selected from the group consisting of -OH, -OCH₃, -CH₂CH₃, -OCH₂COOH, -CH₂COOH, OC(CH₂)₃-COOH.

viii)

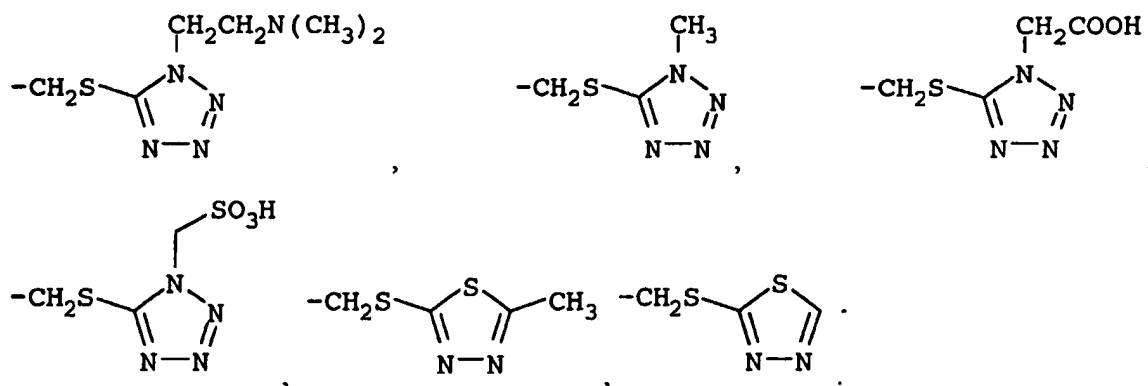


15 wherein:

R_{18} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms; preferably it is selected from the group consisting of: PhCH(OH)-, -CH₂CN

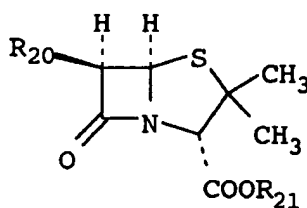


R₁₉ is selected from the group consisting of H and a monovalent radical containing
 5 from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 6 nitrogen atoms and
 from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of:
 CH₃COOCH₂,



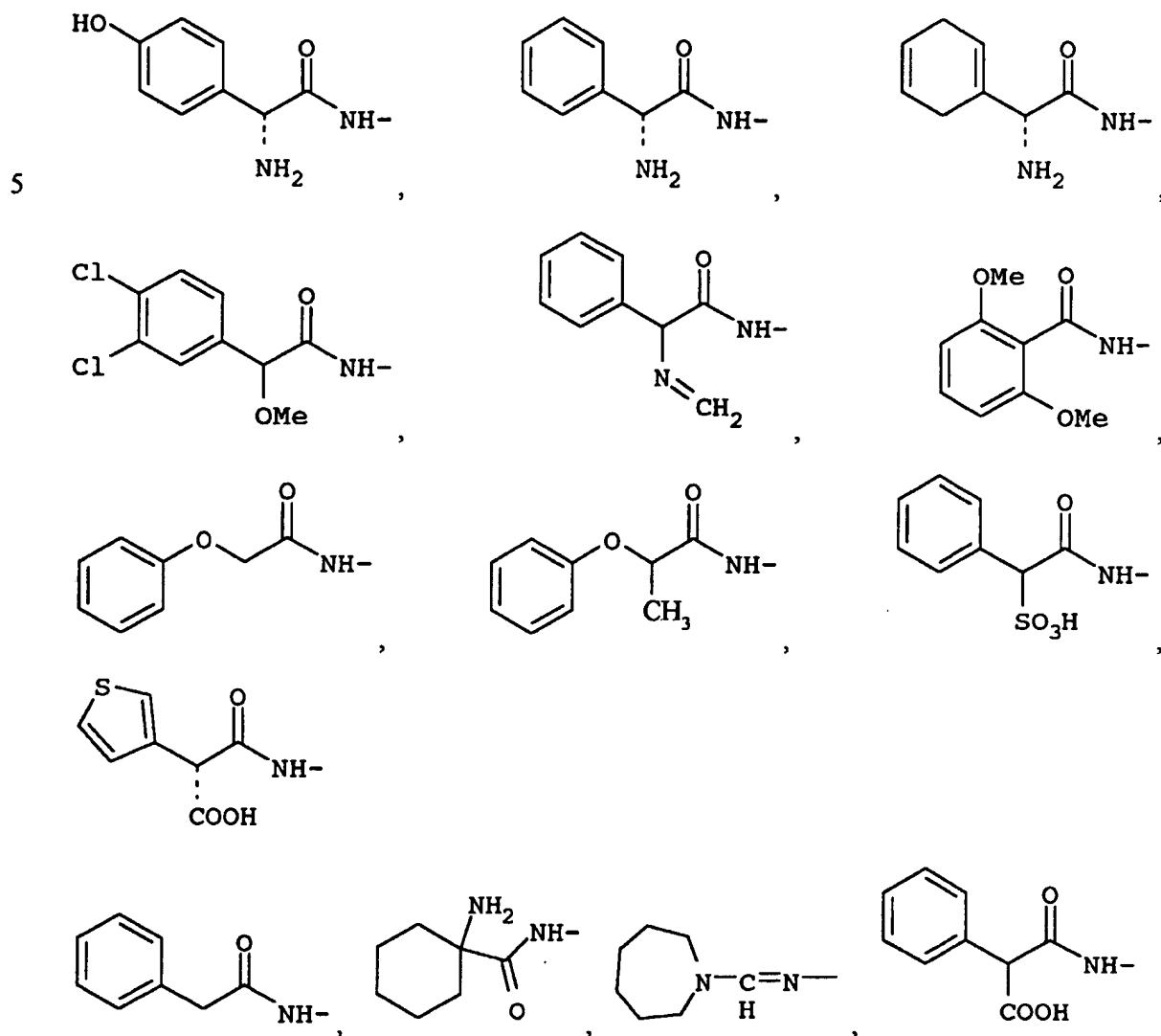
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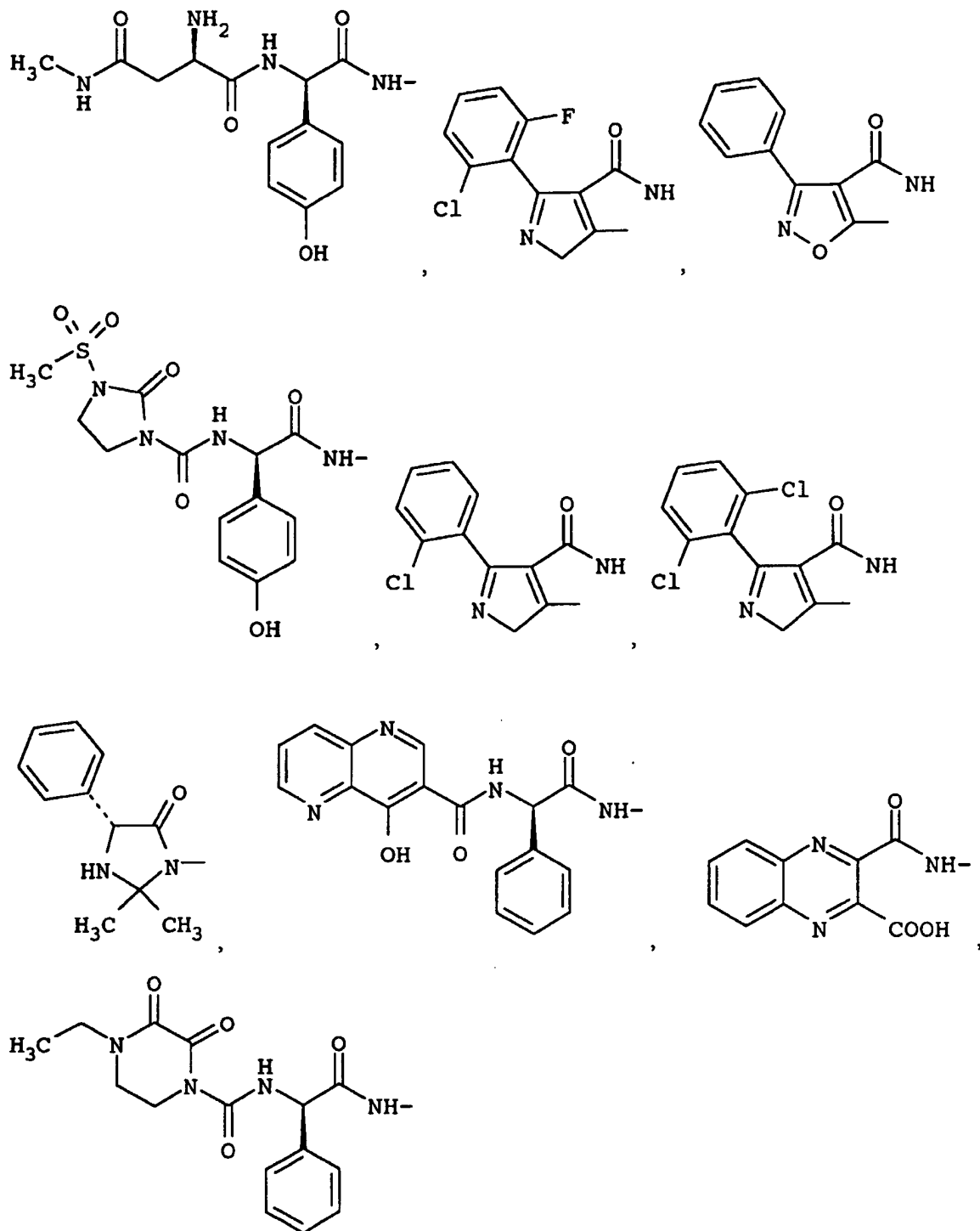
ix)



wherein:

R₂₀ is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms, from 0 to 3 fluorine atoms and from 0 to 3 chlorine atoms; preferably it is selected from the group consisting of:



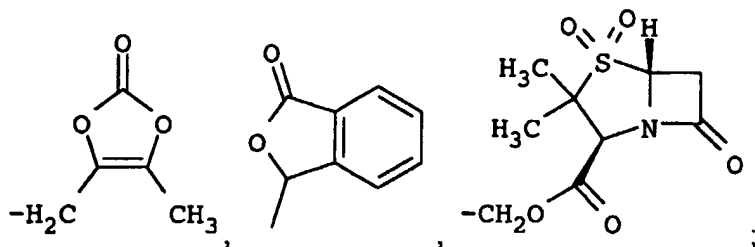


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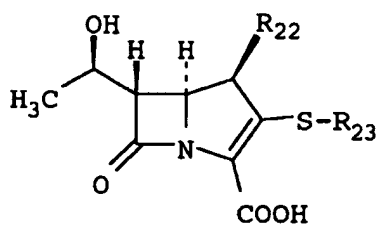
$-HNCO(CH_2)_3\overset{\text{NH}_2}{\underset{\text{NH}_2}{\text{CH}}}\text{COOH}$, $-NHCO(CH_2)_3CH(NH_2)COOH$, $CH_2=CH_2SCH_2CONH-$;

R_{21} is selected from the group consisting of H and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms and

from 0 to 3 sulfur atoms; preferably it is selected from the group consisting of: H, -CH₂OCOC(CH₃)₃, -CH(CH₃)OCOOC₂H₅, -CH₂CH₂N(CH₂CH₃)₂,



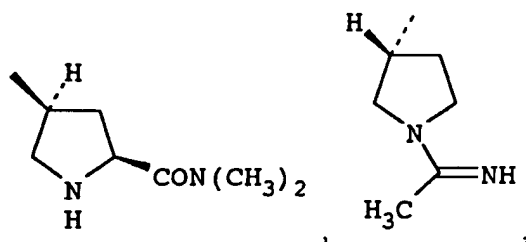
5 x)



wherein:

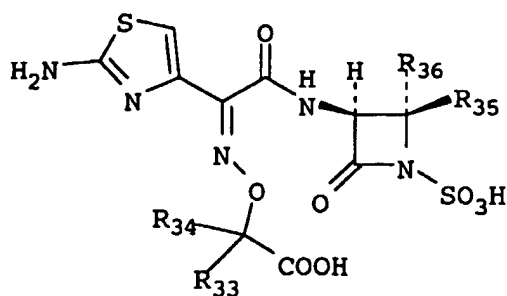
R₂₂ is selected from the group consisting of H and methyl;

R₂₃ a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms and from 1 to 5 nitrogen atoms; preferably it is selected from the group consisting of: -CH₂CH₂NHCH=NH,



xi)

15

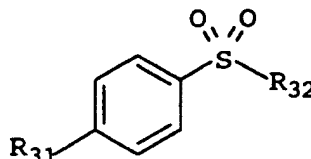


wherein:

R_{33} , R_{34} and R_{36} are independently selected from the group consisting of H and CH_3 ;
 R_{35} is selected from the group consisting of H and $-CH_2OCONH_2$,

5

xii)



wherein:

10 R_{31} is selected from the group consisting of $-NH_2$, $-CH_2NH_2$ and $-NHCH_2Ph$

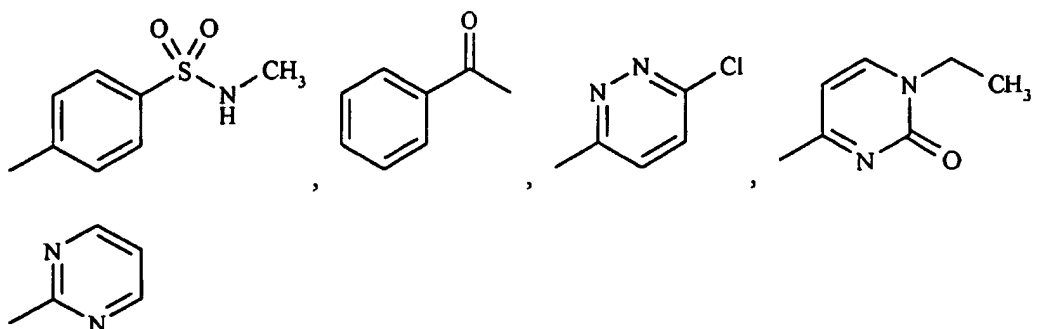
R_{32} is selected from the group consisting of $-NH_2$, $-NHR_{26}$ and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 5 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; wherein R_{26} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

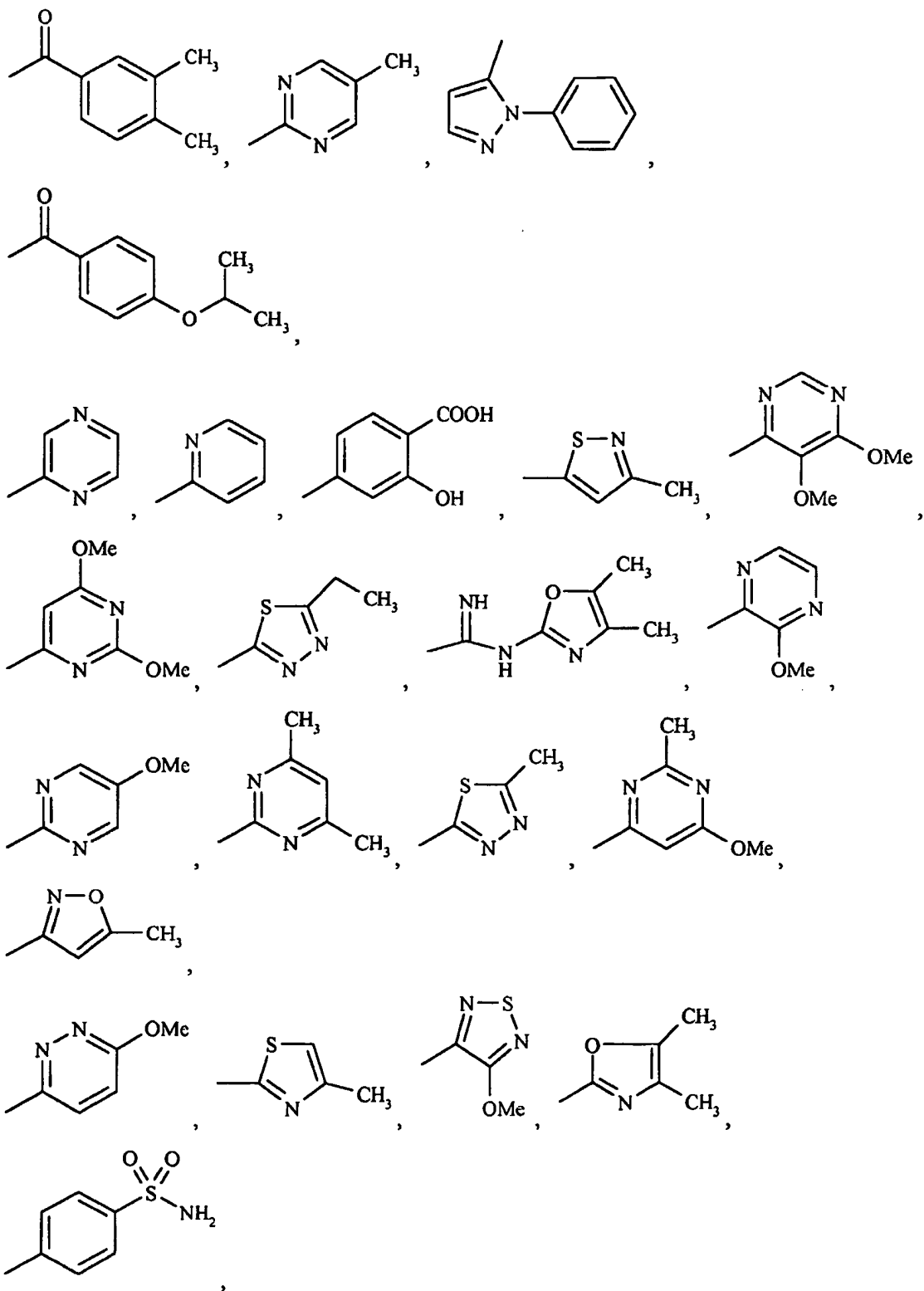
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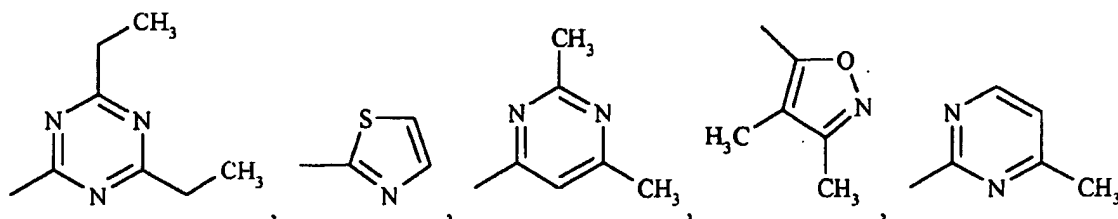
preferably R_{32} is selected from the group consisting of: 4-(2-hydroxyethylamino)phenyl, guanyl, 4-(amino)phenyl, 4-(aminomethyl)phenyl, 4-(carboxymethylamino)phenyl, succinylaminophenyl, 2-amino-5-thiazolyl;

preferred examples of R_{26} are: acetyl, carbamoyl, 3-methyl-2-butenoyl, aminothioxomethylene,

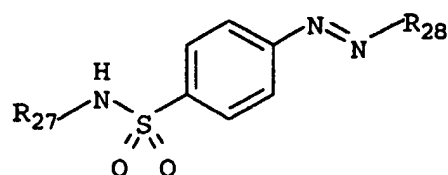
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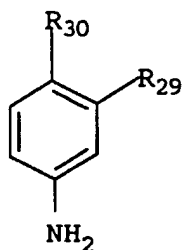
xiii)



wherein:

- 5 R_{27} is selected from the group consisting of H and 4,6-dimethyl-2-pyrimidinyl;
 R_{28} is a phenyl group substituted in at least 2 of the positions 2, 3, 4 and 6 by a group selected from hydroxyl, carboxyl and amino; preferred examples of R_{28} are 2,4-diamino-6-carboxyphenyl, 2,4-diaminophenyl, 3-carboxy-4-hydroxyphenyl;

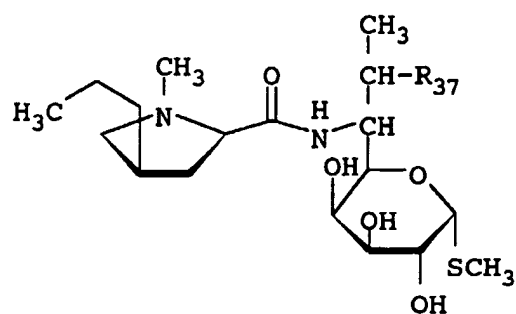
10 xiv)



wherein:

- R_{29} is selected from the group consisting of hydrogen and hydroxyl
 15 R_{30} is selected from the group consisting of carboxyl, phenoxycarbonyl, 4-(amino)phenylsulfinyl, hydrazinocarbonyl;

xv)

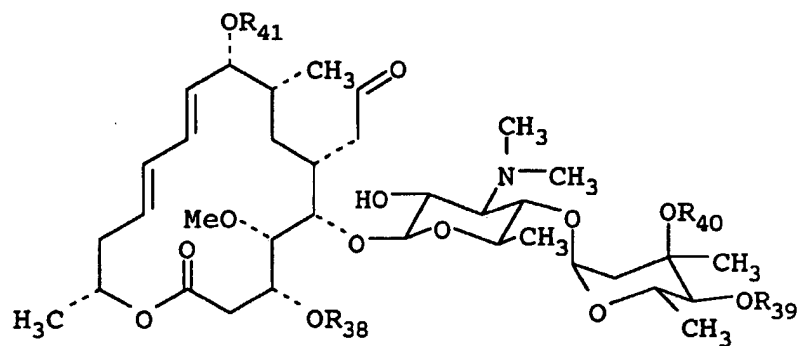


wherein:

R_{37} is selected from the group consisting of Cl and -OH;

5

xvi)



wherein:

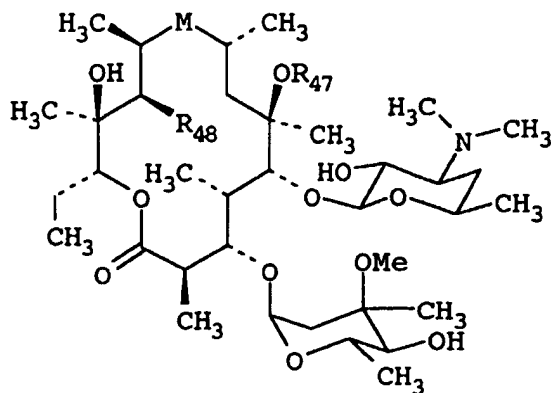
10 R_{38} R_{39} R_{40} are independently selected from the group consisting of H and acyl; preferably they are selected from the group consisting of H acetyl, propionyl, butyryl, valeryl

R_{41} is independently selected from the group consisting of H and



15

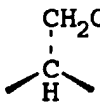
xvii)



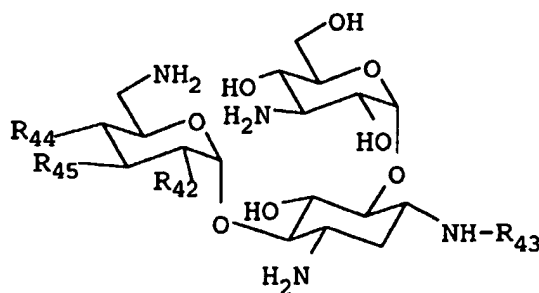
wherein:

R_{47} is selected from the group consisting of H and $-CH_3$

- 5 M is selected from the group consisting of CO, N-methyl-aminomethylene and $-CH(NHR_{49})-$ wherein R_{49} is a substituted methylene bridge connecting N with R_{48}
 R_{48} is hydroxyl or, when M is $-CH(NHR_{49})-$, is $-O-$;

Preferably R_{49} is  ;

10 xvii)

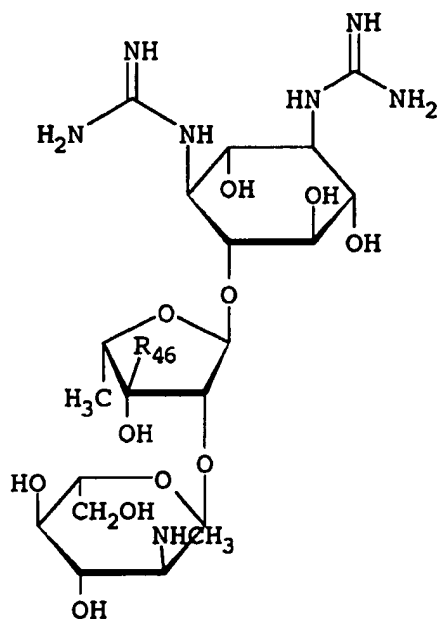


wherein:

R_{42} is selected from the group consisting of hydroxyl and amino;

- 15 R_{43} is selected from the group consisting of hydrogen, (R) and (S)-4-amino-2-hydroxybutyryl
 R_{44} and R_{45} are independently selected from the group consisting of hydrogen and hydroxyl.

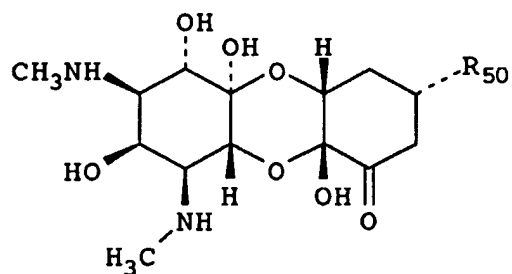
xviii)



wherein:

- 5 R_{46} is selected from the group consisting of $-CH_2OH$ and $-CHO$;

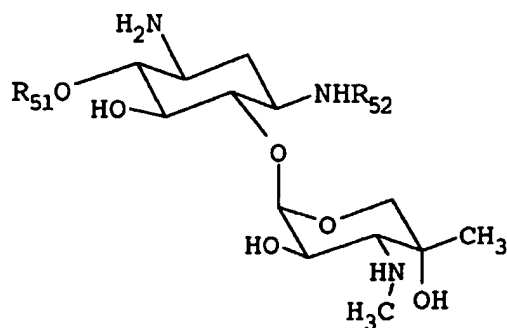
xix)



- 10 wherein:

R_{50} is a C_1 - C_4 alkyl, preferably it is selected from the group consisting of methyl and n-butyl.

xx)

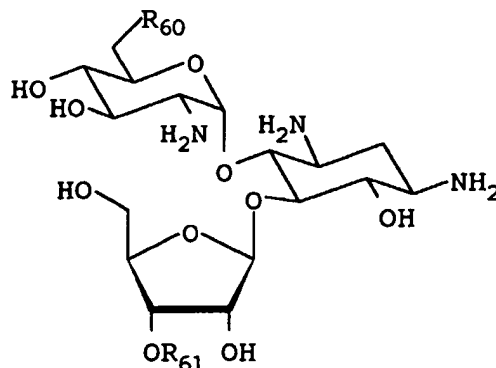


wherein:

R₅₁ is independently selected from the group consisting of 3-amino-6-(aminomethyl)-3,4-dihydro-2H-pyran-2-yl and 2-amino-2,3,4,6-tetra-deoxy-6-(methylamino)- α -D-eritro-hexopyranosyl,

R₅₂ is selected from the group consisting of H and -CH₂CH₃.

xxi)

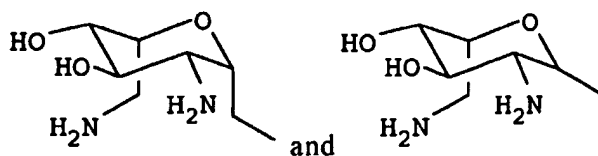


10

wherein:

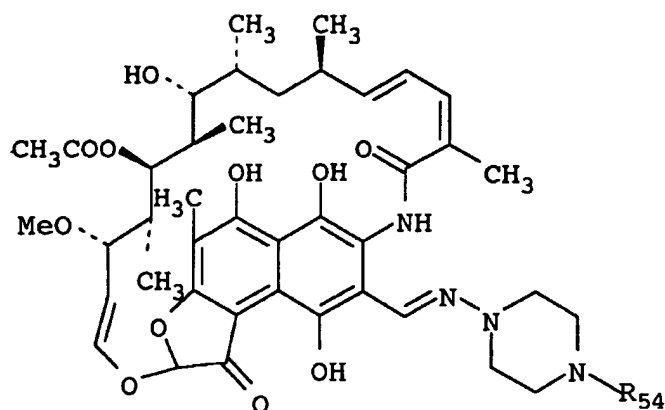
R₆₀ is selected from the group consisting of -OH and -NH₂;

R₆₁ is selected from the group consisting of H,



15

xxii)



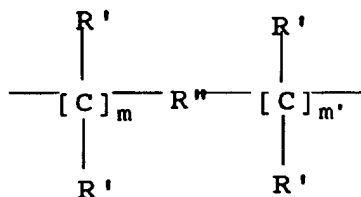
wherein R_{54} is a C_1 - C_4 linear or cyclic alkyl, preferably it is selected from the group consisting of methyl and cyclopropyl.

- 5 In a preferred embodiment X is a divalent radical having the following structure : $(L')_f-X'$, wherein

X' is a divalent radical comprising from 1 to 50 carbon atoms, from 0 to 10 nitrogen atoms, from 0 to 20 oxygen atoms, from 0 to 2 sulfur atoms and from 0 to 8 halogen atoms.

- L' is selected from the group consisting of O, S, NR' and CO; with R' selected from the group consisting of H and linear and branched C_1 - C_4 alkyl;
 10 f is 0 or 1.

In a preferred embodiment X' is represented by the following formula:



- 15 wherein:

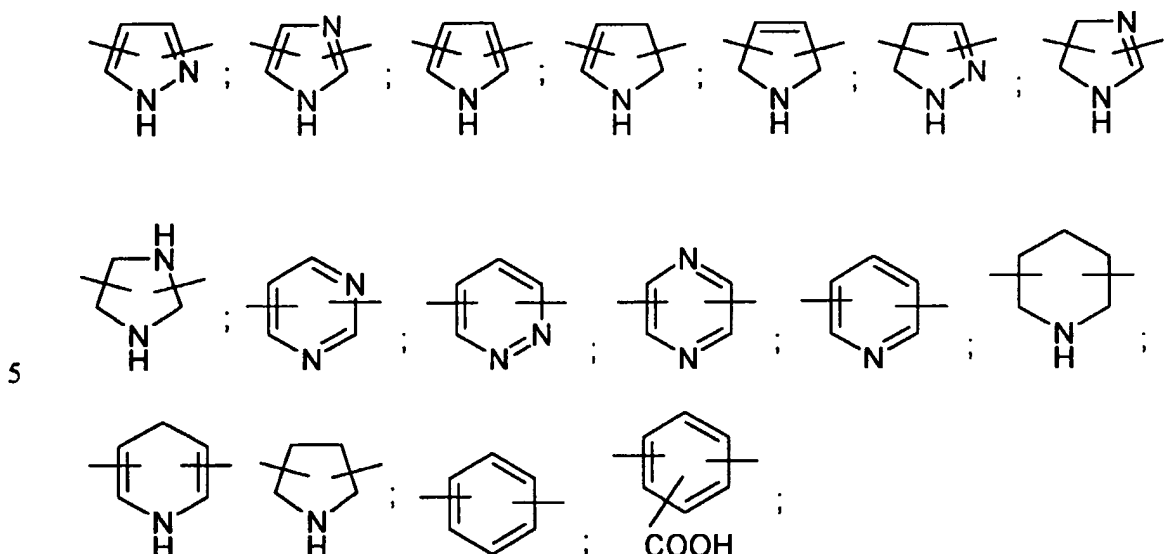
m is selected from 0, 1, 2 and 3; preferably it is 1;

m' is selected from 1, 2 and 3; preferably it is 1;

each R' is independently selected from the group consisting of H, linear and branched C_1 - C_4 alkyl; preferably it is H;

- 20 R'' is selected from the group consisting of: 5 and 6 membered saturated, unsaturated and aromatic heterocycles, phenyl, optionally substituted by a carboxylic group;

When R" is an heterocycle, it is preferably selected from the group consisting of the following divalent radicals:



More preferably R" is selected from the group consisting of a pyridyl and pyrazolyl radical, most preferably it is selected from the group consisting of 2,3-, 2,6- pyridyl and 3, 5-pyrazolyl radicals, wherein 2, 3, 5 and 6 indicate the positions connecting the ring to the carbons of the bridge.

In another preferred embodiment X' is a C₁-C₂₀ alkylene group, preferably C₂-C₆, optionally substituted by -NH₂, -OH, NHCOR^E wherein R^E is selected from the group consisting of methyl, ethyl, linear or branched C₃-C₅ alkyl; a C₅-C₇ cycloalkylene group, optionally substituted by one or more C₁-C₆ alkyl chains;

15 In a third preferred embodiment X' is selected from the group consisting of a group of formula :

-CHR^{'''}-CHR^{'''}-(O-CHR^{'''}-CHR^{'''})_p- and -CHR^{'''}-CHR^{'''}-CHR^{'''}-(O-CHR^{'''}-CHR^{'''}-CHR^{'''})_p-
 wherein each R^{'''} is independently selected from the group consisting of H and CH₃
 p varies from 1 to 6, preferably from 1 to 4.

20 In another preferred embodiment the group X comprises a radical having specific antioxidant properties as disclosed in WO 00/61537, WO 00/61541, WO 00/61604.

Non limiting examples of compounds from which the antioxidant radical is derived are: Aspartic acid, Histidine, 5-Hydroxytryptophan, 4-Thiazolidincarboxylic acid, 2-Oxo-4-thiazolidincarboxylic acid, 2-Thiouracil, 2-Mercaptoethanol, Esperitine, Secalciferol, 1-α-OH-vitamin D₂, Flocalcitriol, 22-Oxacalcitriol, 24,28-Methylene-1α-hydroxyvitamin D₂, 2-Mercaptoimidazol, Succinic acid,

- L-Carnosine, Anserine, Selenocysteine, Selenomethionine, Penicillamine, N-Acetylpenicillamine, Cysteine, N-acetyl-cysteine, Glutathione or its esters, Gallic acid, Ferulic acid, Gentisic acid, Citric acid, Caffeic acid, Hydrocaffeic acid, p-Coumaric acid, Vanillic acid, Chlorogenic acid, Kynurenic acid, Syringic acid, Nordihydroguaiaretic acid,
- 5 Quercetin, Cathechin, Kaempferol, Sulphurethyne, Ascorbic acid, Isoascorbic acid, Hydroquinone, Gossypol, Reductic acid, Methoxyhydroquinone, Hydroxyhydroquinone, Propyl gallate, Saccharose, Vitamin E, Vitamin A, 8-Quinolol, 3-ter-Butyl-4-hydroxyanisole, 3-Hydroxyflavone, 3,5-ter-Butyl-p-hydroxytoluene, p-ter-Butyl-phenol, Timolol, Xibornol, 3,5-di-ter-Butyl-4-hydroxybenzyl-thioglycolate, 4'-Hydroxybutyranilide, Guaiacol, Tocol,
- 10 Isoeugenol, Eugenol, Piperonyl alcohol, Allopurinol, Conyferyl alcohol, 4-Hydroxyphenetyl alcohol, p-Coumaric alcohol, Curcumin, N,N'-Diphenyl-p-phenylenediamine, Ethoxyquin, Thionine, Hydroxyurea, 3,3'-Thiodipronic acid, Fumaric acid, Dihydroxymaleic acid, Thiocitic acid, 3,4-Methylendioxy-cinnamic acid, Piperonylic acid, N-Ethylendiethanolamine, Thiodiethylenglycol.
- 15 The following are non-limiting example which illustrate the invention.

Experimental

Example 1

- 20 Male Guinea pigs (weighing 300 to 500 g) were killed by a blow on the neck and exsanguinated. Urinary bladders were cut into strip preparations (3x12 mm). Guinea-pig bladder strips were rapidly transferred to jacketed tissue baths (25 ml) and mounted between two hooks. One of the hooks was connected to a force transducer (Gould UC2). The strips were maintained at 37°C in a physiological salt solution (PSS) that contains the following
- 25 components: NaCl (119 mM), KCl (4.6 mM), CaCl₂ (1.5 mM), MgCl₂ (1.2 mM), NaHCO₃ (20 mM), NaH₂PO₄ (1.4 mM) and glucose (11 mM). The solution was gassed with a 95/5 mixture of O₂/CO₂ until a pH of 7.4 was achieved. A tension of 0.5 g was initially applied to each preparation. During stabilization (40-60') the strips were repeatedly washed and the tension was adjusted. Tissue contraction was induced by corbachol 3×10^{-6} M.
- 30 The experiment compares the inhibition of contraction obtained by using a solution of the composition according to the invention with the effect achieved by the same drug without cyclodextrin. Both the composition and the drug were dissolved in dimethylsulphoxide (DMSO) and then added to the tissue bath where their concentration was 1.0×10^{-5} M.

The drug used is 2-fluoro- α -methyl[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy) butyl ester (NO-1).

F1 and F2 represent the following compositions:

F1: 1.340 g of α CD and 0.500 g of NO-1 mixed in water and then dried.

5 F2: 1.820 g of dimethyl β CD and 0.500 g of NO-1 mixed in water and then dried.

F0 represents the comparative test performed by using NO-1 alone (no CD).

The percentage of inhibition of contraction obtained were the following:

Composition	Inhibition (%)
F1	26.05
F2	31.52
F0 (comparative)	21.67

Example 2

Male Guinea pigs (weighing 300 to 500 g) were killed by a blow on the neck and exsanguinated. The thoracic aorta artery was isolated, placed in a ice cold PPS that contains the following components: NaCl (119 mM), KCl (4.6 mM), CaCl₂ (1.5 mM), MgCl₂ (1.2 mM), NaHCO₃ (20 mM), NaH₂PO₄ (1.4 mM) and glucose (11 mM), cleaned of connective tissue and cut into transverse ring (3mm). Each ring was then suspended vertically in the organ chamber (25 ml) and mounted between two hooks in PPS maintained at 37°C and gassed with a mixture 95/5 of O₂/CO₂ until achievement of a pH 7.4. One of the hooks was connected to a force transducer (Gould UC2). A resting tension of 2 g was initially applied to each preparation. During stabilization (45') the strips are repeatedly washed and the resting tension is adjusted.

Aorta rings were precontacted with phenylephrine 3×10^{-6} M and exposed to the drug at a concentration 1.0×10^{-6} M.

The experiment compares the inhibition of contraction effect achieved by using a solution of the composition according to the invention with the effect achieved by the same drug without cyclodextrin. Both the composition and the drug were dissolved in dimethylsulphoxide (DMSO).

25 The drug used is 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester (NO-2).

F1, F2 and F3 represent the following compositions:

F1: 1.470 g of α CD and 0.500 g of NO-2 mixed in water and then dried.

F2: 1.470 g of α CD and 0.500 g of NO-2 mixed in ethanol/water and then dried.

F3: 2.000 g of dimethyl β CD and 0.500 g of NO-2 mixed in water and then dried.

F0 represents the comparative test performed by using NO-2 alone (no CD).

The percentages of inhibition obtained were the following:

Composition	Inhibition (%)
F1	54
F2	59
F3	61
F0 (comparative)	19

Claims

1. Composition comprising cyclodextrins and a NO-releasing drug of formula

5



wherein A is the radical deriving from a drug;

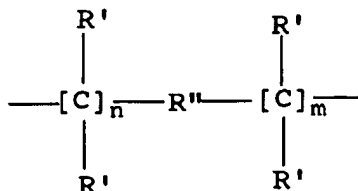
X is a divalent radical connecting A with the NO-releasing group L-NO_n;

L is selected from the group consisting of: O, S and NH;

n is 1 or 2.

- 10 2. Composition according to claim 1 wherein -L-NO_n is -O-NO₂
3. Composition according to claims 1-2 wherein the cyclodextrin is selected from the group consisting of α CD, dimethyl α CD, trimethyl-α CD, β CD, dimethyl-β CD, trimethyl-β CD, 2-hydroxypropyl-β CD, 3-hydroxypropyl-β CD, 2,3-dihydroxypropyl-β CD, γ CD, dimethyl γ CD, trimethyl γ CD and polymeric CD.
- 15 4. Composition according to claim 1-3 wherein the drug is selected from the following compounds: non steroidal antiinflammatory and analgesic drugs, antibacterial (antibiotics), antiviral, steroids, antineoplastic, β-adrenergics (agonists and blockers), antihyperlipoproteinemic, bone resorption inhibitors.
5. Composition according to claim 1-4 wherein X is a divalent radical having the following structure: (L')_f-X', wherein X' is a divalent radical comprising from 1 to 20 carbon atoms, from 0 to 5 nitrogen atoms, from 0 to 5 oxygen atoms, from 0 to 2 sulfur atoms and from 0 to 5 halogen atoms and L' is selected from the group consisting of O, S, NR', CO, with R' selected from the group consisting of H, linear and branched C₁-C₄ alkyl; f is 0 or 1
- 20 6. Composition according to claim 5 wherein X' is represented by the following formula:

25



wherein:

n is selected from 0, 1, 2 and 3; preferably it is 1;

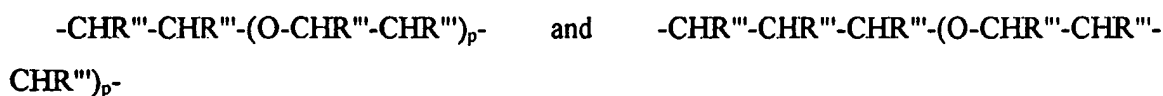
30

m is selected from 1, 2 and 3; preferably it is 1;

each R' is independently selected from the group consisting of H, linear and branched C_1 - C_4 alkyl; preferably it is H;

R'' is selected from the group consisting of: 5 and 6 membered saturated, unsaturated and aromatic heterocycles, phenyl, optionally substituted by a carboxylic group.

- 5 7. Composition according to claim 5 wherein X' is a C_1 - C_{20} alkylene group, preferably C_2 - C_6 , optionally substituted by $-NH_2$, $-OH$, $NHCOR^E$ wherein R^E is selected from the group consisting of methyl, ethyl, linear or branched C_3 - C_5 alkyl; a C_5 - C_7 cycloalkylene group, optionally substituted by one or more C_1 - C_6 alkyl chains;
8. Composition according to claim 5 wherein X' is selected from the group consisting of a
10 group of formula :

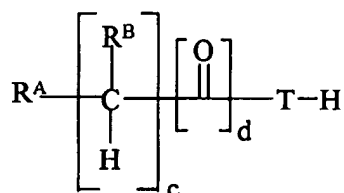


wherein each R''' is independently selected from the group consisting of H and CH_3

p varies from 1 to 6, preferably from 1 to 4.

- 15 9. Composition according to claims 1-8 wherein the drug is selected from the following formulas

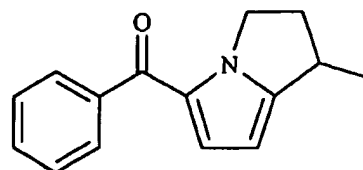
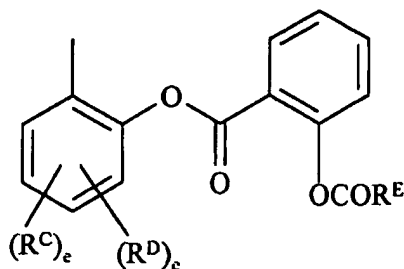
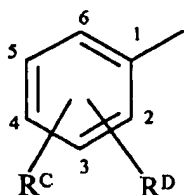
i)



where c and d are independently 0 or 1;

- 20 T is selected from the group consisting of: O, NH and S;

R^B is selected from the group consisting of H, a linear or branched C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl; When c is equal to 0, d is 1, R^A is selected from the group consisting of:



wherein:

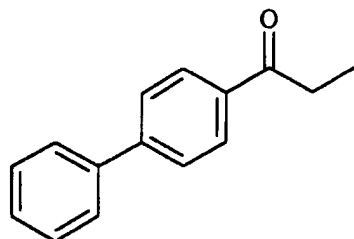
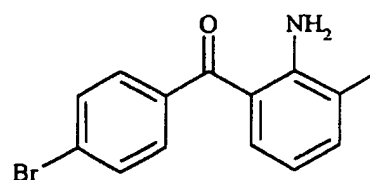
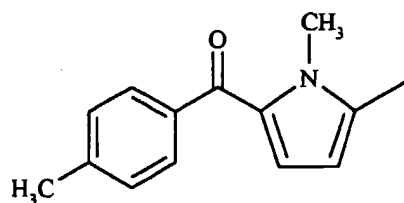
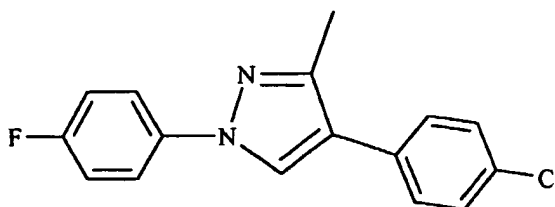
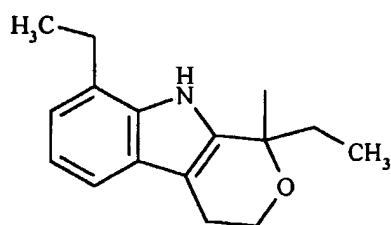
R^C is selected from the group consisting of amino, $R^E\text{CONH-}$, OCOR^E group, and the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from the group consisting of O, N, and S;

R^E is selected from the group consisting of methyl, ethyl and a linear or branched C_3 - C_5 alkyl;

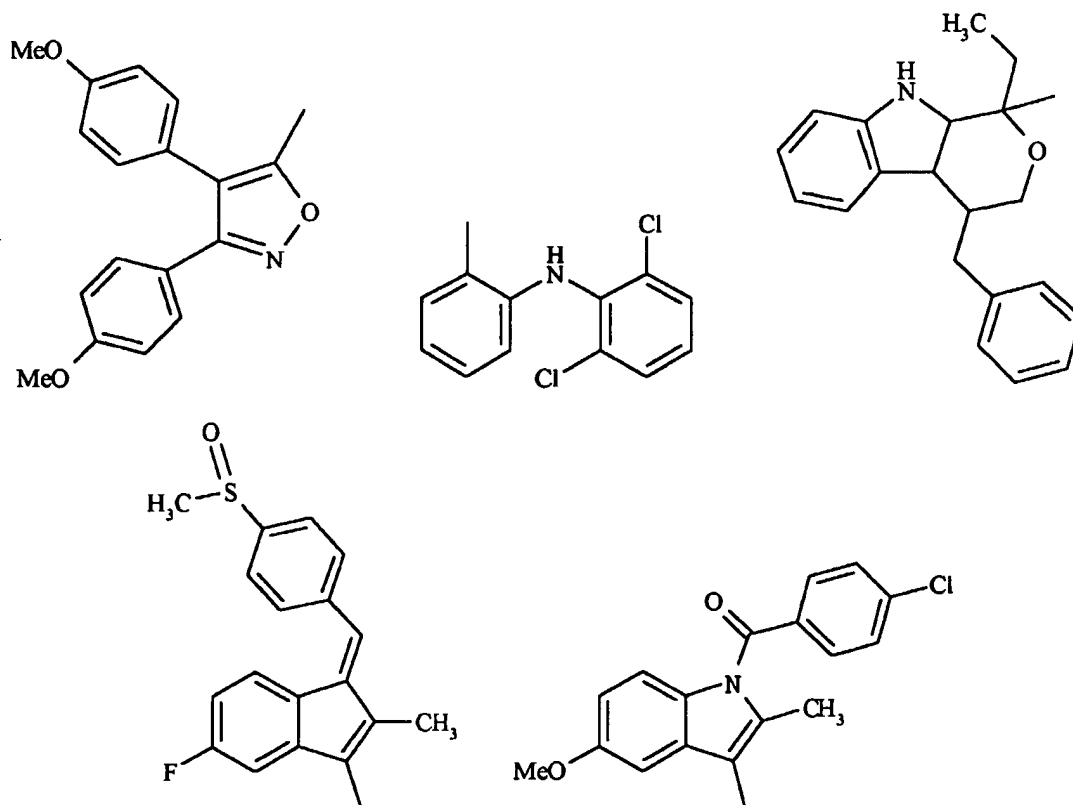
R^D is H, OH, halogen, a linear or when permissible branched alkyl having 1 to 4 atoms, a linear or when permissible branched alkoxy having 1 to 4 atoms, a linear or when permissible branched perfluoroalkyl having 1 to 4 carbon atoms, for example trifluoromethyl, amino, mono- or di- $(C_1$ - $C_4)$ alkylamino;

e is 0 or 1;

when c is equal to 1, d is equal to 1, R^B is hydrogen, R^A is selected from the group consisting of:

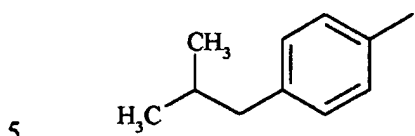
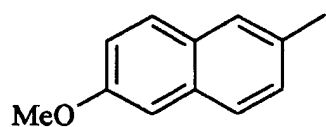
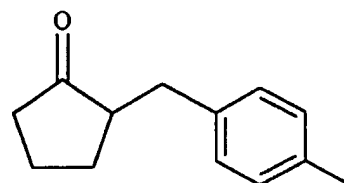
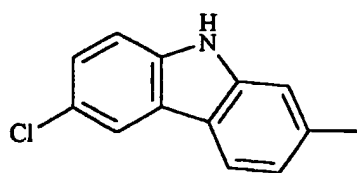
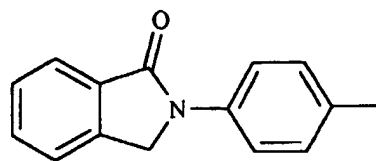
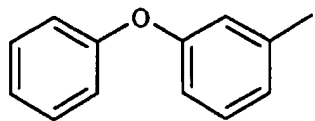


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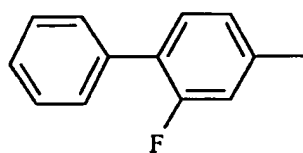
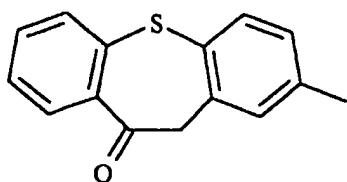
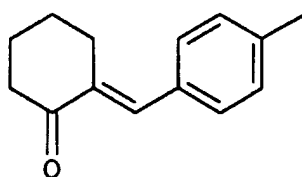
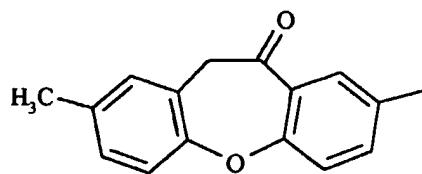
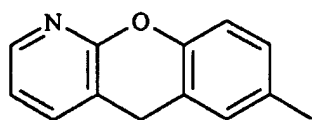


5 when c is equal to 1, d is equal to 1 and R^B is CH_3 , R^A is selected from the group consisting of:



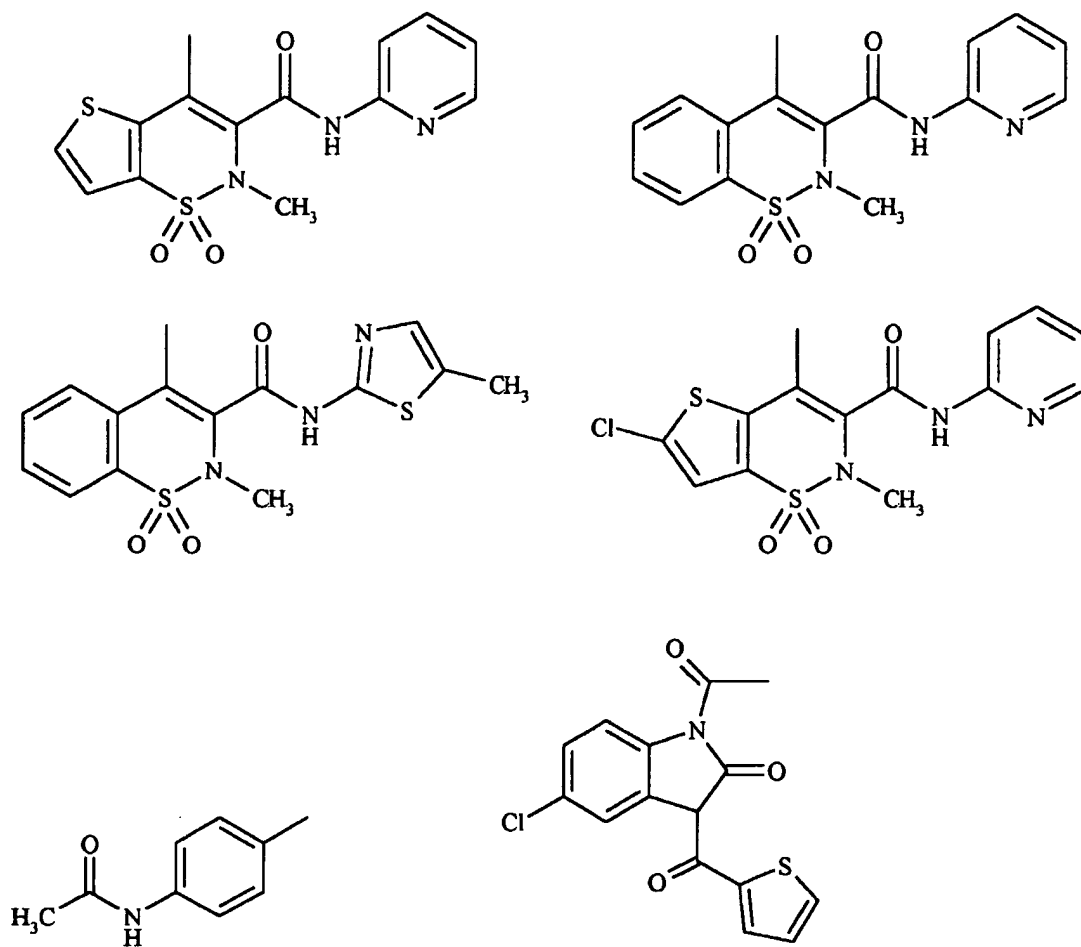


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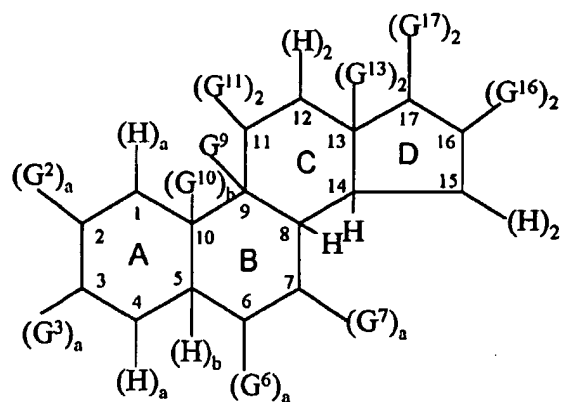
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when **c** is equal to 0, **d** is equal to 0, **R^A** is selected from the group consisting of:



5

ii)



wherein:

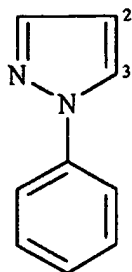
10 at the position 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 5-10 there may be a double bond; the ring A is optionally an aromatic ring;

a is equal to 1 or 2, **b** is equal to 0 or 1;

each **G**² is independently selected from the group consisting of H, Cl, Br;

each **G**³ is independently selected from the group consisting of H, O-CH₃, O-CH₂-CH₂-Cl, OH; two **G**³ can form a carbonyl group with the C³ atom;

5 one **G**² and one **G**³ can unite to form a ring of formula



wherein C²=C³ are part of the steroid structure;

each **G**⁶ is independently selected from the group consisting of H, Cl, F, CH₃, -CHO;

each **G**⁷ is independently selected from the group consisting of H, Cl, OH;

10 each **G**⁹ is independently selected from the group consisting of H, Cl, F;

G¹⁰ is selected from the group consisting of H, Cl, F, CH₃, -CHO;

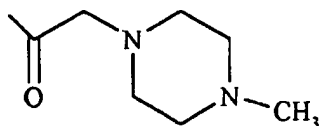
each **G**¹¹ is independently selected from the group consisting of H, OH, , Cl; two **G**¹¹ can form a carbonyl group with the C¹¹ atom;

each **G**¹³ is independently selected from the group consisting of H, CH₃;

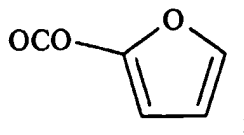
15 each **G**¹⁶ is independently selected from the group consisting of H, CH₃, OH; two **G**¹⁶ can form a vinyl group with the C¹⁶ atom;

each **G**¹⁷ is independently selected from the group consisting of H, OH and a monovalent radical comprising from 1 to 20 carbon atoms and from 0 to 5 oxygen, sulfur, nitrogen, halogen atoms; preferably it is H, OH, CH₃, C≡CH, CO-R-OH, CO-RH, CO-R-Cl, OCO-RH, CO-COO-RH, R-COOH, CH(OH)R-OH, COO-R-Cl, OC(O)O-RH, CO-R-SH, CO-R-O-CO-R-N(CH₂CH₃)₂, CO-SCH₂F, CO-R-OCORH,

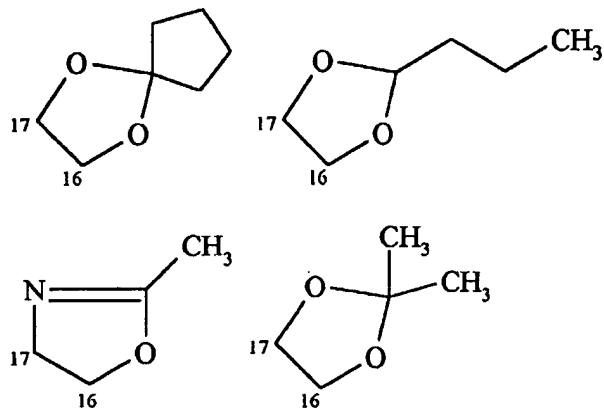
20



wherein R is a C₁-C₂₀ linear or branched alkylene radical, and

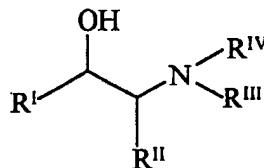


two G^{17} can form a carbonyl group with the C^{17} atom;
 one G^{16} can unite with a G^{17} group to form, together with C^{16} and C^{17} the following groups:



5

iii)



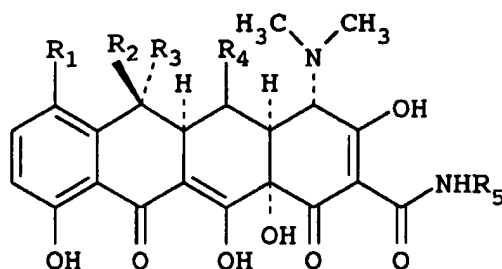
R^I is monovalent radical comprising from 6 to 20 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, chlorine, bromine, fluorine;

R^{II} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms;

R^{III} is selected from the group consisting of hydrogen and linear or branched alkyl having from 1 to 4 carbon atoms;

R^{IV} is selected from the group consisting of hydrogen, a linear or branched alkyl having from 1 to 4 carbon atoms and a substituted aryl; preferably R^{IV} is selected from the group consisting of tert-butyl and isopropyl;

iv)



wherein:

R₁ is selected from the group consisting of H, Cl and dimethylamino,

5 **R₂** is selected from the group consisting of H, OH,

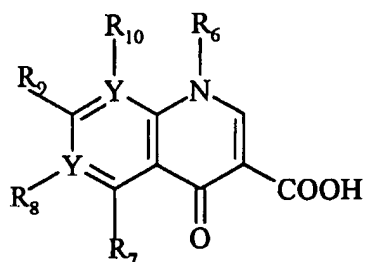
R₃ is selected from the group consisting of H, CH₃,

R₂ and **R₃** together can be a methylene group (CH₂=),

R₄ is selected from the group consisting of H, OH,

10 **R₅** is selected from the group consisting of H, CH₂OH and a monovalent radical containing from 5 to 20 carbon atoms and from 1 to 8 nitrogen atoms; the radical can further comprise other functional groups such as carboxyl and hydroxyl.

v)



15

wherein

each **Y** is independently selected from the group consisting of C and N,

R₆ is selected from the group consisting of cyclopropyl, phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-fluoroethyl and ethyl;

20 **R₇** is selected from the group consisting of H, amino, methyl,

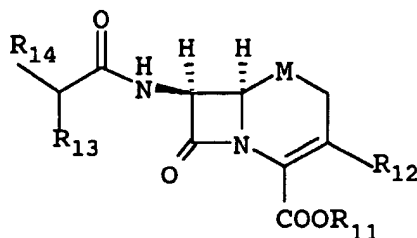
R₈ is selected from the group consisting of H and F;

R₉ is selected from the group consisting of H, methyl and a monovalent radical containing from 1 to 20 carbon atoms and from 1 to 4 nitrogen atoms;

R₁₀ is selected from the group consisting of H, Cl and F;

R_6 e R_{10} can unite to form an optionally substituted six membered ring optionally containing up to two heteroatoms selected from the group consisting of oxygen and sulfur:

5 vi):



wherein

M is selected from the group consisting of sulfur, carbon or oxygen;

10 **R₁₁** is selected from the group consisting of H, pivaloyloxymethyl,

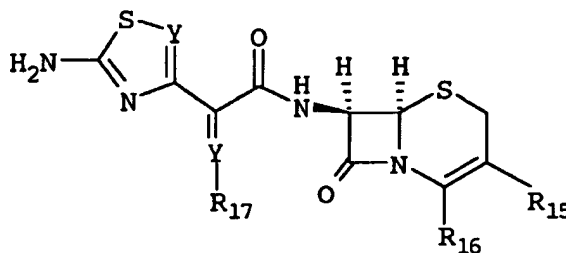
R₁₂ is selected from the group consisting of chlorine and a monovalent radical containing from 1 to 5 carbon atoms, from 0 to 5 nitrogen atoms and from 0 to 1 sulfur atoms;

15 **R₁₃** is selected from the group consisting of amino, hydroxyl and monovalent radical containing from 1 to 10 carbon atoms, from 0 to 5 oxygen atoms and from 0 to 5 nitrogen atoms; preferably it is selected from the group consisting of amino, hydroxyl, carboxyl and

R₁₄ is an unsaturated C₆ ring, optionally substituted;

20

vii)



wherein:

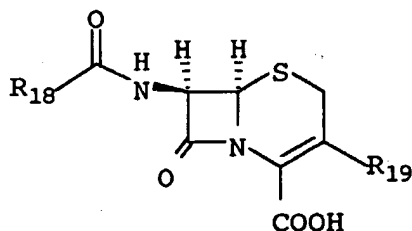
each Y is independently selected from the group consisting of carbon and nitrogen

R₁₅ is selected from the group consisting of hydrogen and a monovalent radical containing from 1 to 12 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms;

R₁₆ is a monovalent radical containing from 1 to 10 carbon atoms and from 2 to 8 oxygen atoms; preferably it is selected from the group consisting of carboxyl, (CH₃)₃CCOOCH₂OCO- and (CH₃)₂CHOCOOCH(CH₃)OCO-; when **R₁₅** is a quaternary ammonium cation, **R₁₆** is optionally a -COO⁻;

R₁₇ is selected from the group consisting of -OH and a monovalent radical containing from 1 to 12 carbon atoms and from 0 to 4 oxygen atoms, preferably it is selected from the group consisting of -OH, -OCH₃, -CH₂CH₃, -OCH₂COOH, -CH₂COOH, OC(CH₂)₃-COOH.

viii)

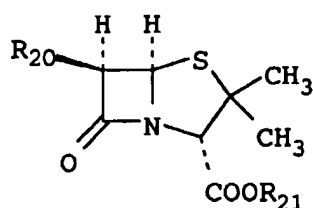


wherein:

R₁₈ is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

R₁₉ is selected from the group consisting of H and a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms, from 0 to 6 nitrogen atoms and from 0 to 3 sulfur atoms;

ix)

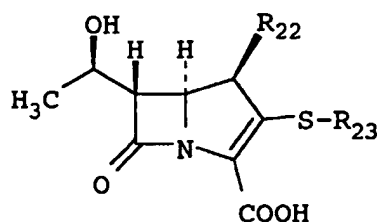


wherein:

R₂₀ is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms, from 0 to 3 fluorine atoms and from 0 to 3 chlorine atoms;

R₂₁ is selected from the group consisting of H and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms;

x)

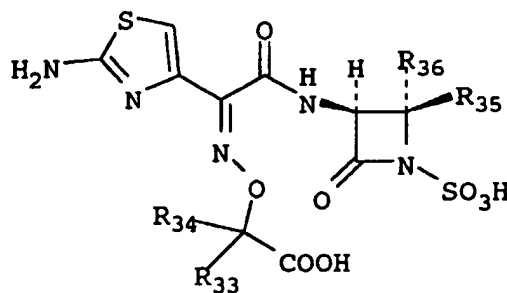


wherein:

R₂₂ is selected from the group consisting of H and methyl;

R₂₃ a monovalent radical containing from 1 to 10 carbon atoms, from 0 to 4 oxygen atoms and from 1 to 5 nitrogen atoms;

xi)

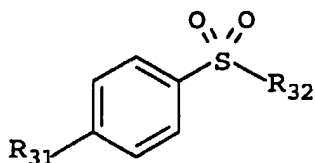


wherein:

R_{33} , R_{34} and R_{36} are independently selected from the group consisting of H and CH_3 ;

R_{35} is selected from the group consisting of H and $-CH_2OCONH_2$,

5 xii)



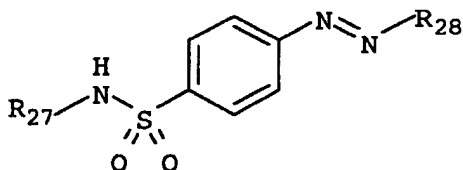
wherein:

R_{31} is selected from the group consisting of $-NH_2$, $-CH_2NH_2$ and $-NHCH_2Ph$

10 R_{32} is selected from the group consisting of $-NH_2$, $-NHR_{26}$ and a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 5 oxygen atoms, from 0 to 5 nitrogen atoms and from 0 to 3 sulfur atoms; wherein R_{26} is a monovalent radical containing from 1 to 20 carbon atoms, from 0 to 8 oxygen atoms, from 0 to 5 nitrogen atoms, from 0 to 3 sulfur atoms and from 0 to 3 chlorine atoms;

15

xiii)



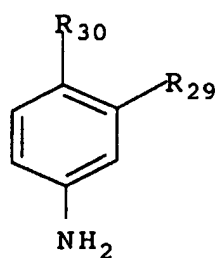
wherein:

R_{27} is selected from the group consisting of H and 4,6-dimethyl-2-pyrimidinyl;

20 R_{28} is a phenyl group substituted in at least 2 of the positions 2, 3, 4 and 6 by a group selected from hydroxyl, carboxyl and amino;

xiv)

46

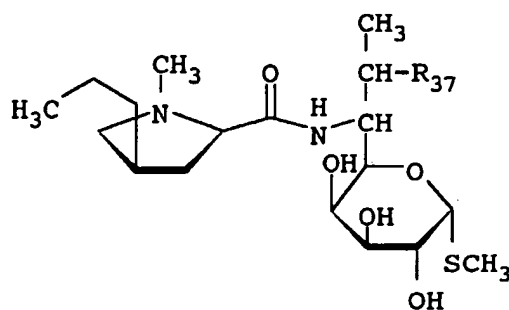


wherein:

R₂₉ is selected from the group consisting of hydrogen and hydroxyl

5 **R₃₀** is selected from the group consisting of carboxyl, phenoxycarbonyl, 4-(amino)phenylsulfinyl, hydrazinocarbonyl;

xv)

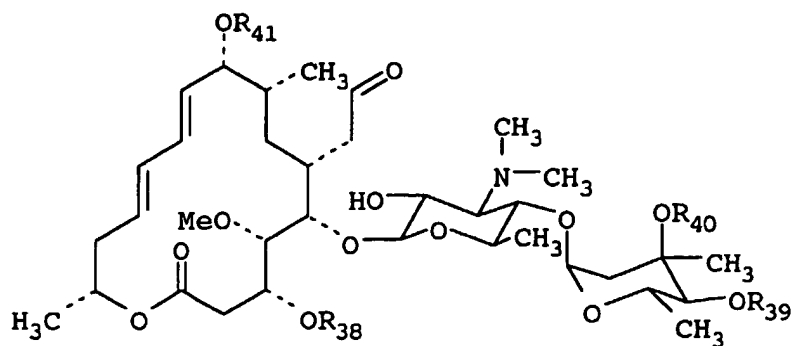


10

wherein:

R₃₇ is selected from the group consisting of Cl and -OH;

xvi)

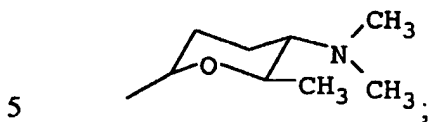


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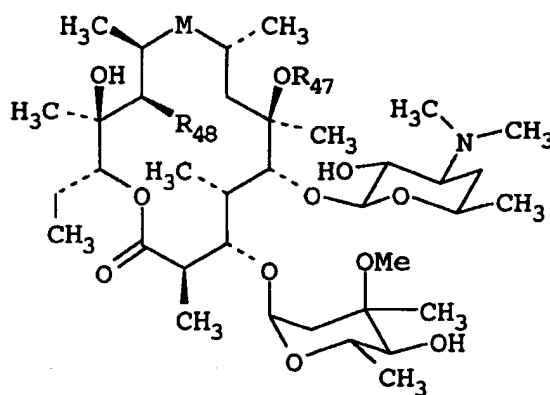
wherein:

R₃₈ **R₃₉** **R₄₀** are independently selected from the group consisting of H and acyl; preferably they are selected from the group consisting of H, acetyl, propionyl, butyryl, valeryl

R₄₁ is independently selected from the group consisting of H and



xvii)

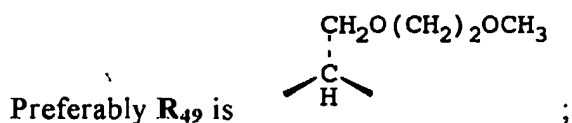


10 wherein:

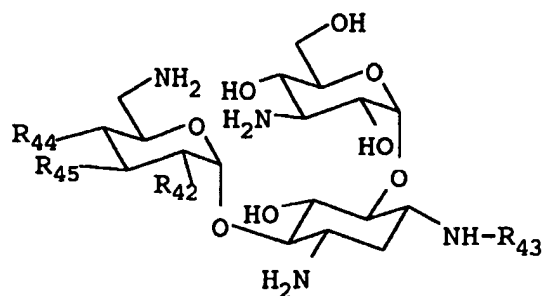
R₄₇ is selected from the group consisting of H and -CH₃

M is selected from the group consisting of CO, N-methyl-aminomethylene and -CH(NHR₄₉)- wherein **R₄₉** is a substituted methylene bridge connecting N with **R₄₈**

15 **R₄₈** is hydroxyl or, when **M** is -CH(NHR₄₉)-, is -O-;



xvii)



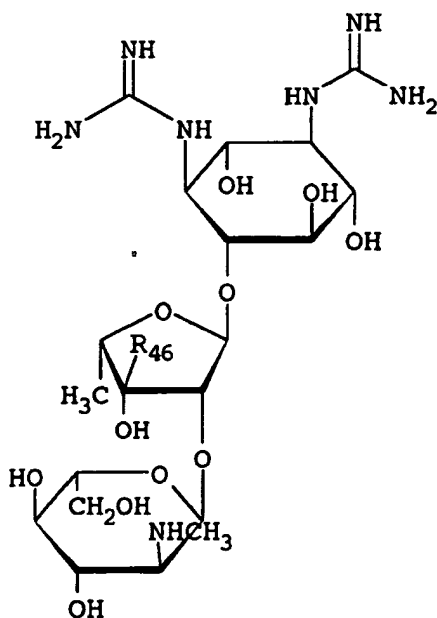
wherein:

R₄₂ is selected from the group consisting of hydroxyl and amino;

5 **R₄₃** is selected from the group consisting of hydrogen, (R) and (S)-4-amino-2-hydroxybutyryl

R₄₄ and **R₄₅** are independently selected from the group consisting of hydrogen and hydroxyl.

10 xviii)

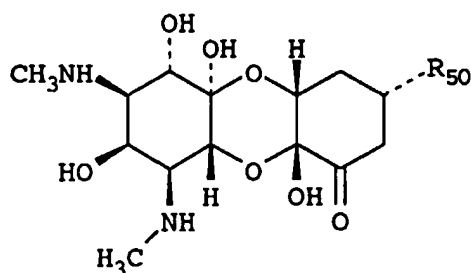


wherein:

R₄₆ is selected from the group consisting of -CH₂OH and -CHO;

15

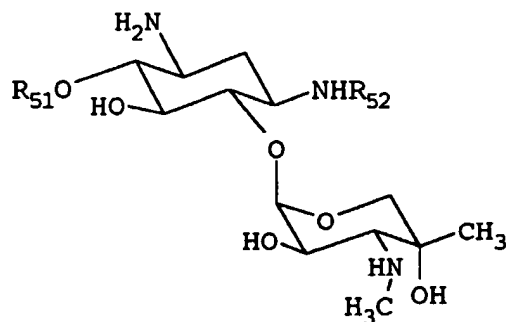
xix)



wherein:

R₅₀ is a C₁-C₄ alkyl, preferably it is selected from the group consisting of methyl and n-butyl.

xx)

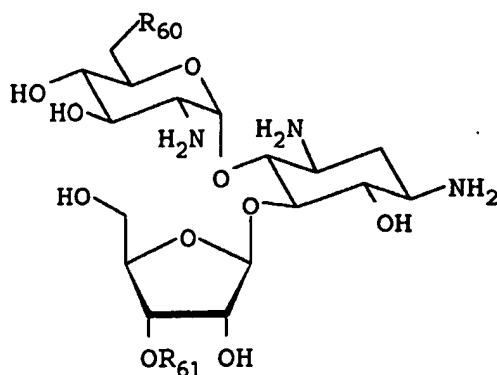


10 wherein:

R₅₁ is independently selected from the group consisting of 3-amino-6-(aminomethyl)-3,4-dihydro-2H-pyran-2-yl and 2-amino-2,3,4,6-tetra-deoxy-6-(methylamino)- α -D-eritro-hexopyranosyl,

R₅₂ is selected from the group consisting of H and -CH₂CH₃.

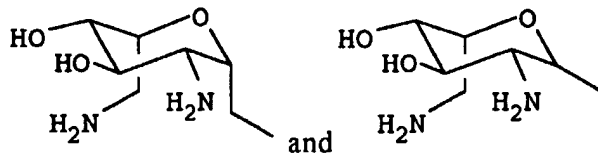
15 xxi)



wherein:

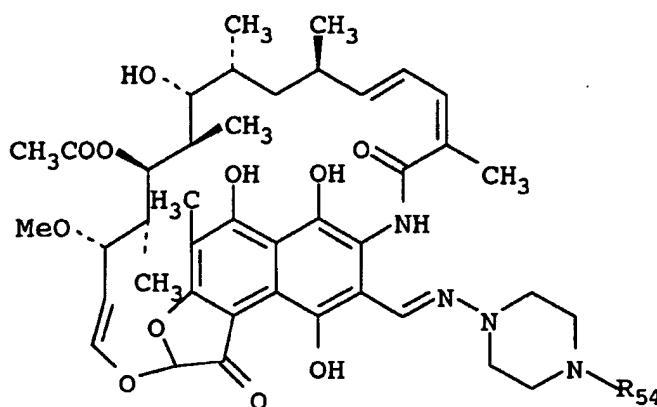
R_{60} is selected from the group consisting of $-OH$ and $-NH_2$;

R_{61} is selected from the group consisting of H ,



5

xxii)



wherein R_{54} is a C_1 - C_4 linear or cyclic alkyl, preferably it is selected from the group consisting of methyl and cyclopropyl.

- 10 10. Composition according to claim 8 wherein the drug is selected from the group consisting of: Aspirin, Salicylic acid, Mesalamine, Acetylsalicylsalicylic acid, Paracetamol, Etodolac, Pirazolac, Tolmetin, Bromefenac, Fenbufen, Mofezolac, Diclofenac, Pemedolac, Sulindac, Ketorolac, Indomethacin, Suprofen, Ketoprofen, Tiaprofenic acid, Fenoprofen, Indoprofen, Carprofen, Naproxen, Loxoprofen, Ibuprofen, Pranoprofen,
- 15 Bermoprofen, CS-670, Zaltoprofen, Tenoxicam, Piroxicam, Meloxicam, Tenidap, Aceclofenac, Acemetacin, 5-amino-acetylsalicylic acid, Alclofenac, Alminoprofen, Amfenac, Bendazac, α -bisabolol, Bromosaligenin, Bucloxic acid, Butibufen, Cinmetacin, Clidanac, Clopirac, Diflunisal, Ditazol, Enfenamic acid, Etofenamate, Felbinac, Fenclozic acid, Fendosal, Fentiazac, Fepradinol, Flufenamic acid, Flunixin, Flunoxaprofen,
- 20 Flurbiprofen, Glucametacin, Glycol salicilate, Ibuproxam, Isofezolac, Isoxepac, Isoxicam, Lornoxicam, Meclofenamic acid, Mefenamic acid, Metiazinic acid, Niflunic acid, Oxaceprol, Oxaprozin, Oxyphenbutazone, Parsalimide, Perisoxal, Olsalazine, Pirprofen, Protizinic acid, Salacetamide, Salicilamide O-acetic acid, Salsalate, Suxibuzone,

Tiaramide, Tinoridine, Tolfenamic acid, Tropesin, Xenbucin, Ximoprofen, Zomepirac, Tomoxiprol.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/15340

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22) cited in the application claims	1-10
X	WO 95 29172 A (GECZY JOSEPH ;THERABEL RESEARCH SA (BE); CYCLOLAB KFT (HU); SZEJTL) 2 November 1995 (1995-11-02) cited in the application claims	1-10
Y	WO 00 61537 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application claims	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

3 June 2002

Date of mailing of the international search report

11/06/2002

Name and mailing address of the ISA

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Authorized officer

Berte, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/15340

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application claims ----	1-10
Y	WO 00 61604 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) cited in the application claims ----	1-10
E	WO 01 00563 A (NICOX SA ;ANTOGNAZZA PATRIZIA (IT); BENEDINI FRANCESCA (IT)) 4 January 2001 (2001-01-04) claims 1,6 ----	1-10
Y	WO 94 12463 A (HCT HEALTH CARE TRADING LTD ;ARENA BARBARA (IT)) 9 June 1994 (1994-06-09) cited in the application claims ----	1-10
Y	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) cited in the application claims ----	1-10
Y	WO 97 31654 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 4 September 1997 (1997-09-04) claims -----	1-10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-10 relate to an extremely large number of possible compounds. In fact, the claims contain so many variables or possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the examples and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/EP 01/15340

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9821193	A	22-05-1998	IT MI962368 A1	14-05-1998
			AU 729423 B2	01-02-2001
			AU 5551998 A	03-06-1998
			BR 9712959 A	01-02-2000
			WO 9821193 A1	22-05-1998
			EP 0941218 A1	15-09-1999
			HU 0000667 A2	28-07-2000
			JP 2001507676 T	12-06-2001
			US 6242432 B1	05-06-2001
WO 9529172	A	02-11-1995	HU 70750 A2	30-10-1995
			AT 197708 T	15-12-2000
			AU 694219 B2	16-07-1998
			AU 2415995 A	16-11-1995
			BG 61974 B1	30-11-1998
			BG 100313 A	31-07-1996
			BR 9506155 A	16-04-1996
			CA 2163539 A1	02-11-1995
			CN 1128028 A ,B	31-07-1996
			CZ 9503163 A3	15-05-1996
			DE 69519463 D1	28-12-2000
			DE 69519463 T2	28-06-2001
			DK 705255 T3	11-12-2000
			EP 0705255 A1	10-04-1996
			ES 2153897 T3	16-03-2001
			FI 956156 A	20-12-1995
			HR 950249 A1	31-10-1997
			WO 9529172 A1	02-11-1995
			JP 9503546 T	08-04-1997
			LT 95133 A ,B	25-10-1996
			LV 11543 A	20-10-1996
			LV 11543 B	20-12-1996
			MD 950440 A	31-10-1997
			NO 955283 A	22-12-1995
			NZ 285149 A	26-06-1998
			PL 312183 A1	01-04-1996
			PT 705255 T	31-05-2001
			RO 114449 B1	30-04-1999
			RU 2136698 C1	10-09-1999
			SI 705255 T1	30-04-2001
			SK 155195 A3	07-05-1997
			US 5698535 A	16-12-1997
WO 0061537	A	19-10-2000	IT MI990753 A1	13-10-2000
			AU 4400100 A	14-11-2000
			BR 0009702 A	08-01-2002
			WO 0061537 A2	19-10-2000
			EP 1169294 A2	09-01-2002
			NO 20014927 A	13-12-2001
WO 0061541	A	19-10-2000	IT MI990752 A1	13-10-2000
			AU 4547400 A	14-11-2000
			BR 0009703 A	08-01-2002
			WO 0061541 A2	19-10-2000
			EP 1169298 A2	09-01-2002
			NO 20014928 A	13-12-2001
WO 0061604	A	19-10-2000	IT MI990751 A1	13-10-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCI/EP 01/15340

Patent document cited in search report	Publication date	Patent family members(s)	Publication date
WO 0061604	A	AU 3820100 A BR 0009696 A WO 0061604 A2 EP 1169337 A2 NO 20014925 A	14-11-2000 08-01-2002 19-10-2000 09-01-2002 13-12-2001
WO 0100563	A 04-01-2001	IT MI991402 A1 AU 6264400 A BR 0011831 A WO 0100563 A1 EP 1187803 A1 NO 20016232 A	27-12-2000 31-01-2001 19-03-2002 04-01-2001 20-03-2002 19-12-2001
WO 9412463	A 09-06-1994	IT 1256450 B AT 152092 T AU 676527 B2 AU 5624194 A BR 9307530 A CA 2150229 A1 DE 69310204 D1 DE 69310204 T2 DK 670825 T3 WO 9412463 A1 EP 0670825 A1 ES 2103563 T3 GR 3024018 T3 HU 73773 A2 JP 8504191 T JP 3231043 B2 RU 2127723 C1 US 5621000 A	05-12-1995 15-05-1997 13-03-1997 22-06-1994 25-05-1999 09-06-1994 28-05-1997 20-11-1997 13-10-1997 09-06-1994 13-09-1995 16-09-1997 31-10-1997 30-09-1996 07-05-1996 19-11-2001 20-03-1999 15-04-1997
WO 9530641	A 16-11-1995	IT 1269735 B IT 1274609 B AT 168986 T AT 184589 T AU 702662 B2 AU 2215695 A AU 678063 B2 AU 7809294 A BR 9407749 A BR 9507634 A CA 2173582 A1 CA 2190087 A1 DE 69412109 D1 DE 69412109 T2 DE 69512232 D1 DE 69512232 T2 DK 722434 T3 DK 759899 T3 WO 9509831 A1 WO 9530641 A1 EP 0722434 A1 EP 0759899 A1 ES 2120070 T3 ES 2139199 T3 GR 3032078 T3 HU 74446 A2	15-04-1997 18-07-1997 15-08-1998 15-10-1999 25-02-1999 29-11-1995 15-05-1997 01-05-1995 12-02-1997 23-09-1997 13-04-1995 16-11-1995 03-09-1998 21-01-1999 21-10-1999 24-02-2000 16-11-1998 20-12-1999 13-04-1995 16-11-1995 24-07-1996 05-03-1997 16-10-1998 01-02-2000 31-03-2000 30-12-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/15340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9530641 A		HU 75961 A2	28-05-1997
		JP 9503214 T	31-03-1997
		JP 9512798 T	22-12-1997
		RU 2136653 C1	10-09-1999
		RU 2145595 C1	20-02-2000
		SI 722434 T1	31-12-1998
		SI 759899 T1	31-12-1999
		US 5700947 A	23-12-1997
		US 5861426 A	19-01-1999
		US 5780495 A	14-07-1998
WO 9731654 A	04-09-1997	IT MI960352 A1	26-08-1997
		AU 706591 B2	17-06-1999
		AU 2092497 A	16-09-1997
		BR 9707739 A	27-07-1999
		CA 2247848 A1	04-09-1997
		WO 9731654 A1	04-09-1997
		EP 0904110 A1	31-03-1999
		HU 9900993 A2	28-09-1999
		JP 2000506133 T	23-05-2000